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Toxicological Life Cycle Impact Analysis of Short and Long Chain Perfluorinated Compounds Compared to Impacts of Treatment Techniques

Joshua R. Glass

TOXICOLOGICAL LIFE CYCLE IMPACT ANALYSIS OF SHORT AND LONG CHAIN PERFLUORINATED COMPOUNDS COMPARED TO IMPACTS OF TREATMENT TECHNIQUES

THESIS

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Abstract

Polyfluoroalkyl substances (PFAS) are man-made substances that are used as surfactants in industrial processes and commercial products most notably for the Air Force in aqueous film-forming foam. These compounds were introduced in the 1950s and have since become pervasive throughout industrial and consumer products such as carpet, leather, and paper as well as textiles that repel water, grease, and oils. As the presence of PFAS continues to grow, so do concerns for the toxicological impacts of exposure to these chemicals. Although there is much research into the toxicological impacts of PFAS, there are no regulatory treatment levels within the United States resulting in a lack of guidance for contaminated sites. In order to fill this knowledge gap, I collected data through a comprehensive literature review of published research testing for effective doses of various symptoms. Using methodology and calculations derived from USEtox® software, I analyzed the data to obtain comparable toxic units (CTU) for several short and long chain PFAS including PFOA and PFOS. The CTU values were calculated using varying concentrations of PFAS contamination, which were then compared to published CTU values for negative life cycle impacts of the following treatment technologies: granulated activated carbon treatment, ion exchange treatment, and supply of bottled water. This comparison found that at concentrations less than 10 and 13 parts per trillion for PFOA and PFOS respectively, the benefits of treatment outweigh the impact of PFAS contamination; however, for short chain PFAS, this limit exceed 700 parts per trillion. This research shows that comparing toxicological impact of contaminants to treatment techniques yields a point at which treatment of contaminants will cause greater negative human impact than the contamination would alone. Toxicological risk assessment provides another means of determining treatment levels.

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I would like to express my sincere appreciation to my faculty advisor, Dr. Eric Mbonimpa for his guidance and support throughout the course of this thesis effort. The insight and experience were greatly appreciated. Thank you, Lt Col Eninger, for serving on my committee and providing guidance and expertise in this endeavor. Thank you, Lt Col Hoisington, for serving on my committee and providing guidance and perspective. Finally, I would like to thank Bridgette Glass for the support and grounding throughout this experience.

Joshua R. Glass

I. Introduction

General Issue

Polyfluoroalkyl substances (PFAS) are manufactured substances used as surfactants in industrial processes and commercial products such as aqueous film-forming foam (AFFF) (U.S. DHHS, 2018; U.S. DHHS, 2015). These compounds were introduced into manufacturing in the 1950s and have since become pervasive throughout industrial and consumer products (Vecitis et al., 2009). Major applications of these chemicals include protectants for carpet, leather, and paper as well as textiles that repel water, grease, and oils (3M 1999; Hekster et al., 2003; Schultz et al., 2003). The chemical and thermal stability aid in their repulsion properties which allow these compounds to help reduce friction which made them common in industries such as aerospace, automotive, and electronics (NIH, 2016). PFAS compounds have a completely fluorinated, hydrophobic carbon chain structure (ranging from 4 to 13 carbons) (Estrellan et al., 2010; Post et al., 2012).

The most common perfluorinated compounds are perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) due to their fluorinated carbon chains and their carboxyl or sulfonic groups, respectively (Department of Health and Human Services, 2009; Place & Field, 2012). According to the Department of Health and Human Services, perfluooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS) are the most significant compounds produced in the United States. At the peak of PFOA and PFOS production in 2002 between 15,000 and 500,000 pounds of PFOA and PFOS were produced (DHHS, 2009).

PFAS are categorized by the length of their carbon chain with six carbons in the chain differentiating between short chains (less than six) and long chain PFAS (six or more) (Brendel et al., 2018). Due to growing concerns with toxicity and groundwater persistence, regulation increased and voluntary

reduction in the amount of long chain PFAS used occurred resulting in an increase in production of short chain PFAS as an alternative (Wang, 2013). Short chain alternatives replaced long chain PFAS with minimal impact to technical performance of goods and industrial processes but are often used in higher quantities compared to long chain variants (Poulsen, 2005).

Due to the chemical stability of PFAS, these compounds are persistent in groundwater, do not easily degrade, and pose a significant risk for biomagnification through the food chain (Fromme et al. 2009). The US Environmental Protection Agency (EPA) has listed PFAS, specifically PFOA and PFOS, as a concerning emergent contaminant due to their wide distribution, persistence in groundwater, lack of biodegradation, and toxicity (EPA, 2016). Some potential adverse health effects resulting from PFAS exposure are cancer, decreased birth weight, immunotoxicity, thyroid disease, chronic kidney disease, and decreased sperm count (Rahman et al. 2014). Toxicological assessments have shown correlations between PFAS and adverse health issues such as total cholesterol, glucose metabolism, body mass index, infertility, lowered immune response to vaccinations, and attention deficit hyperactivity disorder (Grandjean et al. 2012, Saikat et al. 2013). Toxicological studies show that children are at an increased risk to exposure of PFAS due to smaller body mass (US EPA, 2009). There is also a risk that PFAS concentrations can be passed from pregnant mothers to their fetuses (EPA, 2016).

In the 1970s, the Air Force began using AFFF with the principle active ingredients of perfluorooctane sulfonate (PFOS) and perfluoroocatanic acid (PFOA) (U.S. Air Force, 2012). By 1985, the DoD bought 75% of the 6.8 million liters of AFFF produced (Moody and Field 2000). In 2016, the Air Force Civil Engineer Center (AFCEC) announced an effort to replace 418,000 gallons of the PFAS AFFF with a new variant, Phos-Chek 3 (AFCEC, 2016). Phos-Chek 3 does not contain PFOS; however, there may be trace amounts of PFOA in this new formula. With 46 years of usage, the extent of contamination is still unknown. PFOS and PFOA have been found in soil, groundwater, and well water at various locations in the DoD (U.S. Air

Force, 2016). As of 2014, there were 290 official military fire training facilities but there are a potential 664 AFFF release locations documented (DoD, 2015; Hu et al., 2016). As a result of the extensive use of PFAS AFFF in the DoD, Air Force installations are beginning to see contamination levels exceed the EPA's Lifetime Health Advisory Levels such as Wright-Patterson Air Force Base near Dayton, Ohio which is used for this research. The Center for Disease Control (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR) will conduct exposure assessments in 2019 to determine the health concerns and extent of contamination for communities near current and former military bases that have known PFAS contamination in drinking water (ATSDR, 2019).

Problem Statement

Due to PFAS's unique physio-chemical properties, there are limited treatment techniques that can effectively remediate PFAS from groundwater and drinking water (Vecitis et al., 2009). However, research shows that granular activated carbon, anion exchange, oxidation, and reverse osmosis show varying but promising degrees of effectiveness (Appleman, 2012). A study for PFAS treatment using ion exchange showed that this treatment was effective and more efficient for removal of short chain PFAS but did not outperform treatment using granular activated carbon (GAC) (Zaggia et al., 2016). Other studies have shown removal of 99% of both PFOS and PFOA using ion exchange with pilot systems and bench scales (Appleman et al., 2014; Dickenson and Higgins, 2016b).

Although GAC, ion exchange, and supplying bottled water to exposed populations are viable options for counteracting PFAS contamination, each of these treatment techniques has an associated life cycle impact to human health (Emery et al., 2019). These life cycle impacts can be compared to the impacts of varying PFAS contaminant concentrations to determine a treatment level.

The objective of my research was to explore risk assessment of short and long chain PFAS as they compare to treatment technologies to determine treatment levels for Air Force installations with PFAS contamination. Specifically, we endeavored to answer:

- How do species used in animal testing impact the human equivalent health impacts?
- What is the difference between various adverse health effects as they relate to the risk assessment model of PFOA and PFOS?
- Do genders differ in toxicological risk assessment of PFOA and PFOS?
- What are the differences in toxicological risk assessment between short and long chain PFAS?
- How do the risks of PFAS contamination compare to life cycle adverse health impact of treatment technologies?

Methodology

I used a USETox® life cycle impact model to determine a comparable toxic unit for short and long chain PFAS. The model incorporated different concentrations of PFAS in drinking water to determine a linear impact model that was used to compare contaminants to treatments garnering a concentration at which the benefits of treatment outweigh the impacts. I then analyzed the model to determine the effect that various animal species, gender, and adverse health symptoms have on the toxicological impacts of PFOA and PFOS. The results from the toxicological model where compared with results or prior investigations of toxicological impact of PFAS treatment technologies at varying concentrations. I analyzed the result from the model to determine treatment levels based on known concentrations.

Scope/Assumptions/Limitations

This study focused on PFAS impacts and PFAS treatment impacts for Wright-Patterson Air Force Base, Ohio. This study was limited by the toxicological animal testing data available for short and long chain PFAS. PFOA and PFOS had sufficient data to perform statistical analyses; however, the short chain PFAS data was limited and therefore were analyzed based on comparisons of means.

Overview

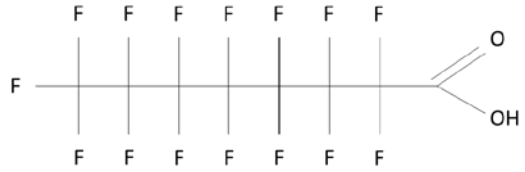
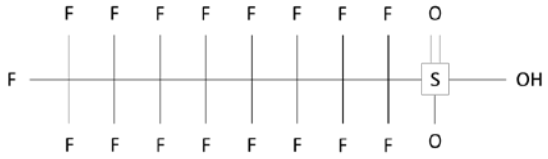
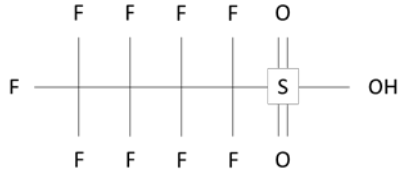
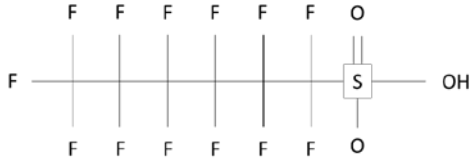
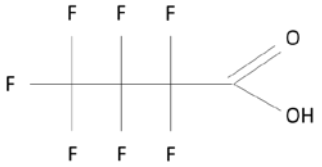
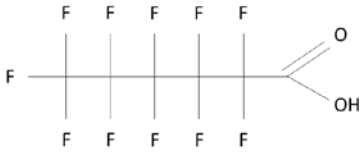
Chapter II reviews existing literature on toxicology of short and long chain PFAS with an emphasis on the concern of PFAS contamination in the Air Force. Chapter II also includes discussion of the risk assessment of PFAS toxicity and life cycle impact assessment as it pertains to PFAS treatment technologies. Chapter III describes procedures for modifying and applying the USEtox® model to develop a risk assessment for PFAS contamination and the methodology used to perform the analysis. Chapter IV presents and analyzes the results from the models and compares those results to prior investigations into the impacts of PFAS treatment technologies. Finally, Chapter V provides conclusions of this study and future research proposals.

II. Literature Review

Polyfluoroalkyl Substances (PFAS)

Polyfluoroalkyl substances are manufactured compounds that are not found naturally used in industrial processes as well as commercial products such as aqueous film-forming foam (AFFF) (U.S. DHHS, 2018; U.S. DHHS, 2015). Production of these compounds began in the 1950s and have since become pervasive throughout industrial and consumer products (Vecitis et al., 2009). Major applications of these chemicals include protectants for carpet, leather, and paper as well as textiles that repel water, grease, and oils (3M 1999; Hekster et al., 2003; Schultz et al., 2003). The chemical and thermal stability aid in their repulsion properties which allow these compounds to help reduce friction which made them common in industries such as aerospace, automotive, and electronics (NIH, 2016). PFAS compounds have a completely fluorinated, hydrophobic carbon chain structure (ranging from 4 to 13 carbons) (Estrellan et al., 2010; Post et al., 2012).

Table 1: Physiochemical Structure of PFAS Chemicals (Rahman et al., 2013)

Carbon Chain Category	Compound Name	Structure
Long Chain	Perfluooctanoic Acid (PFOA)	
Long Chain	Perfluorooctane Sulfonic Acid (PFOS)	
Short Chain	Perfluorobutane Sulfonic Acid (PFBS)	
Short Chain	Perfluorohexane Sulfonic Acid (PFHxS)	
Short Chain	Perfluorobutanoic Acid (PFBA)	
Short Chain	Perfluorohexanoic Acid (PFHxA)	

The most common and massed produced perfluorinated compounds are perfluoroalkyl carboxylic acids (PFCAs) and perfluoroalkyl sulfonic acids (PFSAs) due to their fluorinated carbon chains and their carboxyl or sulfonic groups, respectively (Department of Health and Human Services, 2009; Place &

Field, 2012). PFOA and PFOS are the most significant compounds produced in the United States with peak production consisting of between 15,000 and 500,000 pounds of PFOA and PFOS during 2002 (DHHS, 2009). As such, PFOS and PFOA were the two most manufactured PFAS in the United States and therefore are the most proliferate contaminates in the PFC chemical group (DHHS, 2009). Production of PFAS compounds has significantly declined due to companies phasing out production of several PFAS compounds since 2001 (3M 2007, DuPont 2008). PFOA and PFOS are no longer manufactured within the United States and are not allowed to be imported; however, several other countries are still producing these materials and trace amounts may still be found in imported goods (DHHS, 2018). In addition to the importation of PFOS and PFOA products, the United States still had large stockpiles of materials containing these PFAS in 2012 (Place & Field, 2012). One of these stockpiled materials was aqueous film-forming foams (AFFF), whose use has been linked to increased concentrations of PFOS and PFOA in surface and groundwater (Place & Field, 2012). According to Place and Field (2012), there were no regulations or restrictions for disposal of the approximately 38 million liters of AFFF maintained by the United States government (Place & Field, 2012). The United States Air Force maintained the largest stockpile of AFFF within the US government, stockpiling 11 million liters, and released the PFC-based AFFF directly into the environmental after use (Place & Field, 2012; U.S. Air Force, 2012). Industries have replaced PFOA and PFOS with PFAS compounds that have shorter carbon chains with five or fewer carbons (Wang, 2013). The PFAS compounds with six or more carbons are categorized as long chain PFAS and compounds with less than six carbons categorized as short chain (Brendel et al., 2018). Short chain PFAS are the standard alternative to long chain with the increased regulation and voluntary reduction of long chain PFAS (Wang, 2013). Short chain alternatives can replace long chain PFAS with minimal impact to technical performance of goods and industrial processes but often require higher quantities compared to long chain variants (Poulsen, 2005). This utilization of short chain PFAS is

exhibited with film-forming firefighting foams as well with short-chain PFAS appearing commonly in new AFFF technologies (Hagenaars, 2011).

PFAS Toxicity

The US Environmental Protection Agency (EPA) has listed PFOA and PFOS, as a concerning emergent contaminant due to their wide distribution and prevalence in the environment which is attributed to their chemical stability (EPA, 2016, Fromme et al. 2009). This chemical stability limits degradation and pose a significant risk for biomagnification through the food chain (Fromme et al. 2009). Many studies on the effects of PFCs have been performed on rats; however, research shows that the half-life of PFAS and PFOA in rats resulting in rats not being an ideal species for human equivalent animal testing (Grandjean & Clapp, 2015). The US Environmental Protection Agency (EPA) issued a health advisory stating a maximum limit of the combined concentration of PFOA and PFOS should not exceed 70 parts per trillion in drinking water in order to protect vulnerable populations including children and pregnant or nursing women (USEPA, 2016). Although vulnerable populations may be affected more greatly, exposure to the general population may result in potential health effects such as cancer, decreased birthweight, thyroid disease, and chronic kidney disease (Rahman et al., 2013). Some studies suggest that higher concentrations of PFOA and PFOS can lead to an elevated risk of testicular and kidney cancers (Barry et al, 2013). Furthermore, human toxicological cohort studies have shown a correlation between PFAS and adverse health effects including total cholesterol, glucose metabolism, infertility, lowered immune response, and attention deficit hyperactivity disorder (Grandjean et al, 2012; Saikat et al. 2013). Children are at an increased risk to exposure of PFAS due to smaller body mass of children (US EPA, 2009). There is also a risk that PFOA is carcinogenic and that PFAS concentrations can be passed from pregnant mothers to their fetuses (EPA, 2016a). There may be an elevated risk of developing

testicular and kidney cancers in populations that have increased PFOA blood serum levels, such as those working in or living near PFOA production facilities (Barry et al. 2013).

PFAS use in the US Air Force

In the 1970s, the Air Force began using AFFF with the principle active ingredients being perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) (U.S. Air Force, 2012). AFFF was the fast and effective means to reduce the potential risk to life and property due to the extensive presence of petroleum, oils, and lubricants (POL) such as JP-8 fuel used for aircrafts. These hydrocarbon fuels, which were required to support, and fly aircraft required fast and effective fire extinguishing techniques which AFFF provided (Moody and Field, 2000). The AFFF used most commonly in the DoD was 3M FC-203CF Light Water ™. 3M Light Water ™ is 70% water, 20% glycol butyl ether, and 10% various compounds of fluoroalkyl and sulfate substances with 1% of the total composition being PFAS (Moody et al., 2003). AFFF covers hydrocarbon fires by creating a blanket that suffocates the fire thus eliminating the hydrocarbons ability to burn (Sheinson et al., 2015). In 1985, the DoD bought 75% of the 6.8 million liters of AFFF products produced within the United States for use in both training and emergency situations (Moody and Field 2000). In 2016, the Air Force Civil Engineer Center (AFCEC) announced an effort to replace 418,000 gallons of the PFAS AFFF with a new variant, Phos-Chek 3 (AFCEC, 2016). Phos-Chek 3 does not contain PFOS; however, there may be trace amounts of PFOA in this new formula. With 46 years of usage, the extent of contamination is still unknown; however, PFOS and PFOA have been found in soil, groundwater, and well water at various locations in the DoD (U.S. Air Force, 2016). Research shows that PFAS can be found in leachate from landfills as well (Allred et. al, 2014, 202). Although most Air Force landfills have been shut down, the remnants of these landfills still pose as a risk of additional PFC contamination. PFAS's resistance to biodegradation allows these compounds to persist in the environment for extended periods of time and have been documented to travel extensively

through groundwater (US Environmental Protection Agency, 2016). Contamination is further complicated because AFFF contains proprietary substances which are not clearly disclosed by manufacturers meaning the amount of PFAS in the AFFF used by the Air Force is largely unknown (D'Agostino and Mabury 2014).

Investigations have found that there were 290 official military fire training facilities but there are a potential 664 AFFF release locations documented in 2014 (DoD, 2015; Hu et al., 2016). Air Force installations are beginning to see contamination levels exceeding the EPA's Lifetime Health Advisory Levels as a result of the extensive use of AFFF. Wright-Patterson Air Force Base near Dayton, Ohio and Peterson Air Force Base near Colorado Springs, Colorado have begun efforts to remediate the contamination through treatment and monitoring of drinking water sources (Barber, 2017; Roeder & Rodgers, 2017). Wright-Patterson AFB added 20,000-pound Granular Activated Carbon (GAC) beds in their effort to treat the PFAS contamination (Barber, 2017).

Treatment of PFAS

PFAS's unique physio-chemical properties limit potential treatment techniques that can effectively remediate PFAS from drinking water (Vecitis et al., 2009). EPA's research discovered that neither natural environmental degradation processes nor conventional treatments, such as coagulation, micro- or ultra-filtration, aeration or disinfection, were capable of remediating PFAS (EPA, 2009; Appleman et al., 2013; Rahman et al., 2014). Coagulation treatment with alum resulted in removal efficiencies for PFOA and PFOS of 12% and 32% respectively (Bao et al., 2014). Contamination levels of 500 times the EPA Lifetime Health Advisory Levels were found at a closed fire training site at Wurtsmith AFB in Michigan 10 years after the fire training activities ceased (Moody et al., 2003). This shows that PFAS stays in the environment and that biodegradation isn't an option. Further research has shown that PFOA and PFOS do not react with microbial degradation techniques as well (Rahman et al., 2013). However, research

shows that granular activated carbon, anion exchange, oxidation, and reverse osmosis show varying but promising degrees of effectiveness (Appleman, 2012). But these treatment techniques come at a price; a study by the Minnesota Department of Health found that the GAC treatment system developed to remediate PFAS cost $0.12 per 1000 gallons treated resulting in an additional treatment cost of $120,000 annually (MDH, 2010). GAC treatment produces secondary waste that requires to be disposed through controlled incineration further limiting GAC as a viable option for remediation (EPA, 2009). Research has found ion exchange to be an effective treatment for both short and long chain PFAS but not outperforming treatment using GAC (Zaggia et al., 2016). Other studies have found removal of 99% of both PFOS and PFOA using ion exchange with pilot systems and bench scales (Appleman et al., 2014; Dickenson and Higgins, 2016b). Although many are researching the best way to remediate PFAS contamination, some agencies responded to the EPA's Lifetime Health Advisory Level by supplying bottle water to the population exposed to the contamination of PFOS and PFOA as a temporary, or in some cases, a permanent solution (Emery et al., 2019).

Risk Analysis

According to the World Health Organization (WHO), toxicological risk analysis comprises of risk assessment, risk management, and risk communication. Risk assessment of chemicals is defined as the process of identifying and categorizing hazards, assessing exposure and utilizing those that information to characterize risk (WHO, 2009) WHO defines risk management as the process of analyzing the alternative policies as a result of the risk assessment. This process applies heath protection factors and fair-trade practices factors to the results of the risk assessment to determine the best method to mitigate the risk such as prevention and control options (WHO, 2009). The final aspect of risk analysis, risk communication, is the exchange of information and opinions concerning the risk of different chemicals and the associated factors and perceptions (WHO, 2009). These three components make up

the risk analysis paradigm of the interactions and responsibilities of the risk assessment, risk management, and risk communication (Figure 1).

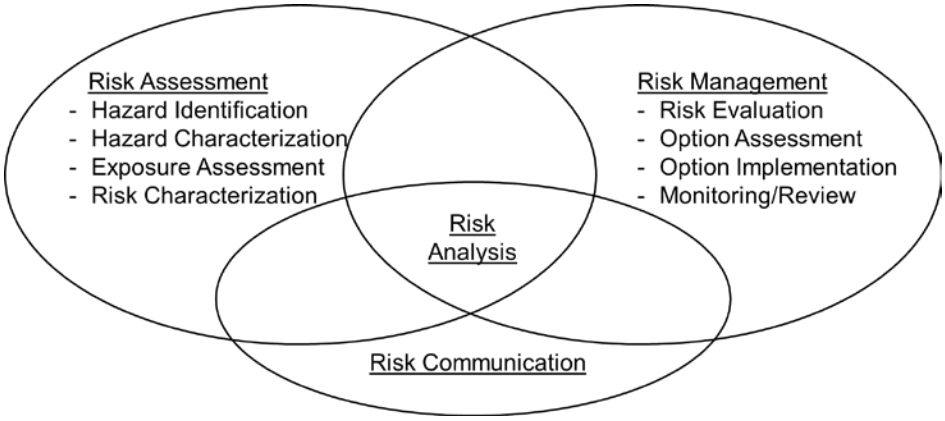


Figure 1: Risk Analysis Paradigm (Adapted from WHO, 2009)

Risk Assessment

Risk assessment is the process of identifying and characterizing hazards, assessing the exposure, and characterizing the risk associated with a chemical. In order to understand risk assessment, two terms must be clearly defined: hazard and risk. According to the World Health Organization, a hazard is a biological, chemical, or physical agent that has the potential to cause an adverse health effect. Risk is defined as the likelihood that exposure to a chemical will cause an adverse health effect and the subsequent severity of that effect (WHO, 2009). However, these definitions are not the consensus among organizations. The International Programme on Chemical Safety (IPCS) defined hazard and risk slightly differently. The IPCS defined hazard as the inherent property of a chemical to cause adverse effects based on exposure to the agent. IPCS defined risk as the probability that specified circumstances of exposure would cause an adverse health effect (IPCS, 2004). This research will focus on the United States Federal Government risk assessment process. The federal government defines risk assessment as justifiably defining health effects that can be directly attributed to exposure to a hazardous material by

an individual or a population (National Research Council, 1993). The National Research Council's risk assessment process follows four steps:

1.) Identify hazards based on whether a chemical can be causally linked to health effects

2.) Dose-response assessment to determine the relation between the exposure and the development of health effects

3.) Exposure assessment to determine the relationship between exposure and regulatory controls

4.) Risk Characterization to describe the combination of the previous three categories including uncertainty (NRC, 1993).

Hazard Identification

Hazard identification is the first step in the risk assessment process. In toxicology, hazard identification focuses on determining if there is enough evidence that a chemical is responsible for the adverse health effects observed (Lammerding and Fazil 2000). The purpose of identifying hazards is to first analyze the nature of health hazards a chemical may cause and then to address the circumstances and exposure that would cause those health hazards (WHO, 2009). The data necessary to identify the hazard of a chemicals can be gathered through various studies and observations such as observations in human or animals, animal tests, in vitro studies, or epidemiological studies.

Animal Studies

Using animals in-place of humans for testing for hazard identification is far from a perfect process; however, animal testing is still regarded as one of the best ways to obtain the necessary data for risk assessment (Barlow et al. 2002). Although animal studies and testing are a best practice, there are significant issues when extrapolating the results to humans (Dybing et al. 2002). The disparities between human and animal tests can be broken down into three categories: the effects contributed to laboratory

environments, disparities between animal and human disease models, and physiological and genetic differences (Akhtar 2015). Several studies have shown that captivity and the artificial environments can cause unintended behavior changes and addition distress in addition to the testing (Suckow et al., 2006; Flow, 1997; Balcombe et al., 2004). These changes can contribute to exacerbated physiological parameters contributing to significantly different results (Baldwin, 2007). Further error can be introduced by the discordance between human and animal models due to a lack of congruence between the two models (Akhtar 2015). Research shows that a conversion between animal and humans can be calculated based on analysis of interspecies variations that can be derived from biological factors such as age, sex, genetic composition, and nutritional status (Vermeire et al., 2001) This extrapolation has been further refined by Huijbregts (2005) to calculate interspecies adjustment factors from animals to human for ingested doses (Equation 1)

Equation 1: Interspecies Adjustment Factor Equation (Huijbregts et al. 2005)

$$\mathrm{AF_a} - \frac{\mathrm{BW_h}^{0.25}}{\mathrm{BW_a}}$$

Where CF_a is the conversion factor for interspecies differences determined by Vermeire et al, BW_h is the average body weight of humans assumed to be 70kg, and BW_a is the average bodyweight of the test species *a* in kilograms. This results in the following table:

Table 2: Interspecies Adjusted Factor from Animal to Human (Adapted from Huijbregts et al., 2005)

Type	$AF_{interspecies}$ (-)	Average Bodyweight (kg)
Human	1.0	70
Pig	1.1	48
Dog	1.5	15
Monkey	1.9	5
Cat	1.9	5
Rabbit	2.4	2

Hen	2.6	1.6
Mink	2.9	1
Guinea	3.1	0.750
Rat	4.1	0.250
Hamster	4.9	0.125
Gerbil	5.5	0.075
Mouse	7.3	0.025

However, these values are based off a rudimentary process and are estimations of the extrapolation factors whereas using species to species physiological difference, species to species non-protein bound fraction of test compounds, kinetic parameters, and tissue-specific gene expression will yield much more specific extrapolation factors (Thiel et al. 2015). Accurate interspecies extrapolation factors are essential for animal tests to be adequate sources of data for hazard identification (Akhtar 2015).

Epidemiology

Another means of assessing risk is through epidemiological studies. Epidemiology is the study of distribution of a disease or other health factors in a human population (Gordis 2014). Epidemiological information are used to develop plans to lessen the impact of illnesses and diseases as well as to develop ways to manage diseases of people who have already developed the illness (Coggon, 2003). According to Gordis (2014), there are five objectives of epidemiology:

1.) Identify the etiology (cause) of an illness or disease and what factors will increase the risk of contracting the disease

2.) Determine the extent of disease within a defined population to develop a management plan

3.) To develop a natural history and severity of a disease to compare future advancements of prevention and management to historic records

4.) To evaluate the current and future preventative measure to analyze the impact of management plans on health outcomes

5.) To develop public policies for disease prevention

To meet the objective of epidemiological studies, three types of studies are commonly used: cross-sectional, case-controlled, and cohort (Gordis, 2014). Cross-sectional studies measure the prevalence of a disease in a defined population at a point in time (Coggon 2003). In these studies, researchers gather historic data on the selected population in order to determine who was exposed to the hazardous chemical and who has not been exposure. From those two groups, they are broken down further into who has the disease and who does not for both those exposure and those not exposed (Figure 2).

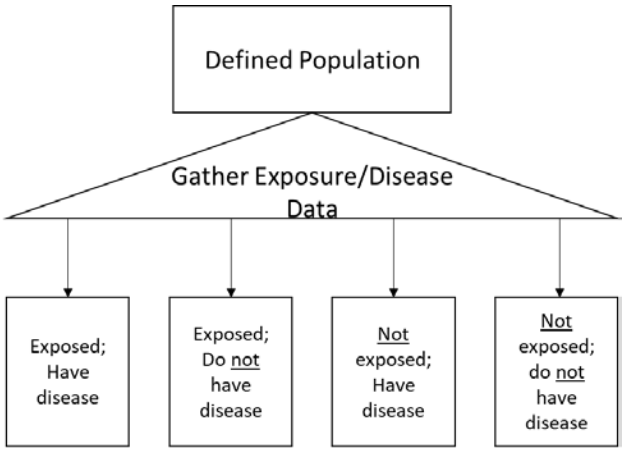


Figure 2: Design of Cross-sectional Epidemiological Study (adapted from Gordis, 2014)

Cross-sectional studies cannot be used to determine what is the cause of the disease and what is the effect of exposure (Coggon, 2003). These studies are limited in establishing a temporal relationship between exposure and outcome as they are designed to show prevalence (Gordis, 2014). To gather a more retrospective understanding of exposure and effect, a case-control study may be performed

(Gordis, 2014). These studies involve selection a group from the population that has the disease and retrospectively analyzing their past to determine their exposure and doing the same with a group that does not have the disease (Coggon, 2014). The major difference between a cross-sectional study and a case-control study is the selection of the groups and the subsequent analysis of their exposure history (Gordis, 2014). A case-control study can be used to show associations between exposure and diseases through the temporal analysis and has the distinct advantage to analyze uncommon disease and their conditions as these studies need relatively few subjects to gather a significant amount of information (Figure 3; Mann, 2003).

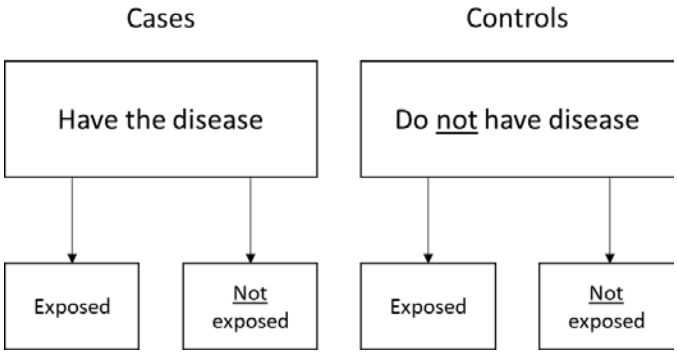


Figure 3: Design of Case-control Study (Adapted from Gordis, 2014)

The final type of epidemiological study commonly used is a cohort study in which researchers select a group of the population that do not have the disease and follow the group forward in time to determine exposure and development of the disease (Figure 4; Gordis, 2014)

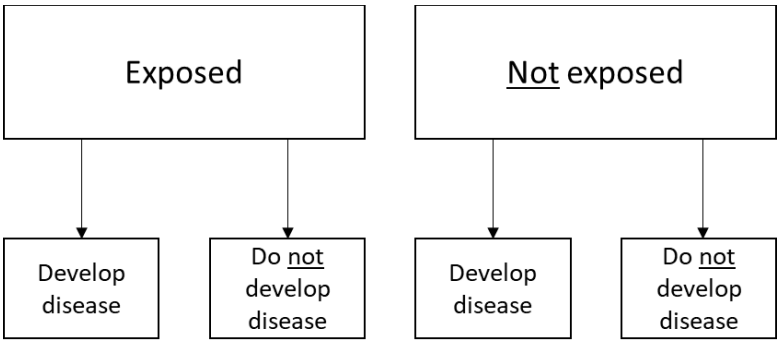


Figure 4: Design of Cohort Study (Adapted from Gordis, 2014)

Prospective cohort studies are common for determining a cause and effect relationship between exposure and the disease and are often a necessary means of obtaining the best epidemiological data because deliberate exposure to hazardous chemicals is unethical (Mann 2003). Cohort studies allow the incidence in both exposure and non-exposed groups to be calculated more accurately than case-controlled studies (Gordis, 2014). These studies also limit the effect of recall bias and selection bias which limit the results of the previous studies (Gordis, 2014). Although each type of study has associated advantages and disadvantages, all epidemiological studies are subjected to the impacts of confounding factors (Gordis, 2014). Confounding factors in epidemiology act the same way as a cofounding factor in any statistical analysis in which a confounding factor is any variable that impacts both the dependent and independent variables causing a spurious association which prevents the determination of correlation or association (Pearl 1998).

Figure 5 shows the impact of a confounding factors in an epidemiological study of pancreatic cancer in which a possible relationship exists between people who drink coffee and people who smoke. Smoking is a known risk factor for pancreatic cancer which may be the result of an observed association

between drinking coffee and pancreatic cancer (Gordis, 2014).

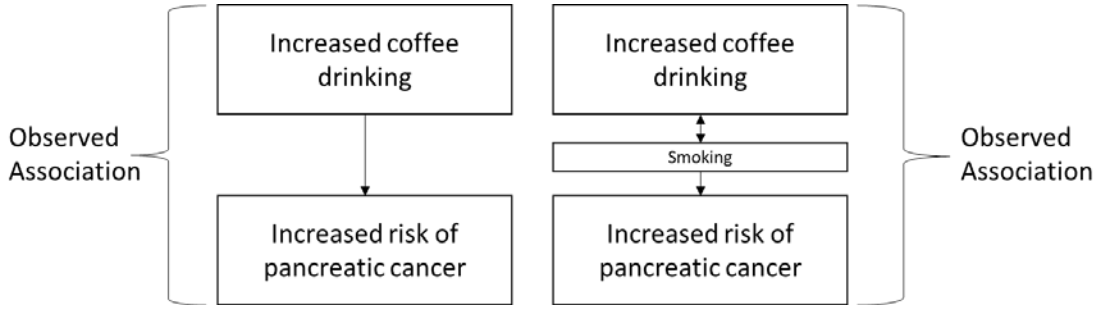


Figure 5: Impact of Confounding Factor (Adapted from Gordis, 2014)

The final aspect of epidemiological studies that needs to be considered is the causal relationship between exposure to a chemical and the development of a disease (Gordis, 2014). According to Sir Austin Bradford Hill (1965), the following nine criteria must be considered when establishing causality:

1.) Strength of association: An association with a large relative risk is more likely to be causal than one that was found to have a weaker relative risk (Nordberg et al. 2019).

2.) Consistency: Several studies conducted separately show signs of association (Nordberg et al. 2019).

3.) Specificity: Causality can be determined if the effect is unique to the exposure of chemical which is rarely the case for most observed diseases (Hill 1965).

4.) Temporality: The research must show that exposure precedes the development of the disease (Nordberg et al. 2019).

5.) Biological gradient: The association demonstrated in a dose-response relationship is confirmed by a studied without evidence of confounding factors (Nordberg et al. 2019).

6.) Biological plausibility: The same results from an epidemiological study are known from animal experiments and can be reproduced (Hill, 1965).

7.) Coherence: There is a corresponding increased observation when exposure is increased such as the increase in lung cancer observed as smoking increased in the population between the 1940s and 1960s (Hill, 1965).

8.) Experiment: The removal of a suspected chemical decreases the amount of observations of the disease (Nordberg et al. 2019).

9.) Analogy: If a similar chemical replaced a known hazard and the same disease was observed, the analogy between the known hazard and the new chemical would support causality (Hill, 1965).

Relative Risk

After epidemiological studies are complete, a relative risk of the hazard can be calculated based on the risk of the health effect and the risk among the group. Relative risk is a measure of scoring and analyzing epidemiological data among different groups (CDC 2012). The relative risk can be calculated by dividing the number of observations of disease in the group exposed to the chemical by the number of observations of the disease in the group that was not exposed to the chemical (Wayne 2018). Relative risk is best used to determine remediation priorities and not levels of risk (WHO, 2009).

Dose-Response Assessment

Following the identification of a hazard, the next step in risk assessment is a dose-response assessment (National Research Council (NRC), 1983). Dose-response data is derived from either in-vivo studies with animals or humans, or in-vitro studies (WHO, 2009). According to the WHO, there are three basic types of doses that can be used to determine a dose-response relationship: external dose, internal dose, and target dose. External dose is the amount of a chemical that is experimentally administered to

an animal or human under controlled conditions that are delivered in specific amounts at specific intervals (WHO, 2009). An external dose is referred to as the exposure of intake dose that is used in epidemiological studies (JECFA). Internal dose is the amount that is adsorbed and enters circulation because of adsorption, distribution, metabolism, or excretion (WHO, 2009). These doses are often obtained through toxicokinetic studies. The final type of dose is a target or tissue dose which is the distribution of a chemical exposure that is present in a targeted or specific tissue of interest (WHO, 2009). The WHO further defines response as the observation or effect seen following exposure to a chemical. The responses typically observed in toxicology are adverse effects which as a change in physiology, growth, development, reproduction, or life span that impair functional capacity of an organism to different degrees (IPCS, 2004). The World Health Organization categorizes responses into four basic categories: quantal response, counts, continuous measures, and ordinal categorical measures (WHO, 2009). Quantal response is when an effect is categorized as either observed or not observed and the response in annotated as the number of subjects that are affected out of the total number exposed (WHO, 2009). Counts are the number of items measured in a single subject such as the number of papillomas on the skin (WHO, 2009). Continuous measures are a quantitative measurement such as body weight (WHO, 2009). Ordinal categorical measures are ordered based on the severity of the observation (WHO, 2009). By graphing the dose and the corresponding response, a distribution curve can be obtained which is typically modified into a logarithmic distribution curve to better display the exponential growth in response as dose increases (Faustman, 1994). In the development of a dose-response curve, several pertinent data points are derived: the no observable adverse effect limit (NOAEL), the lowest observable adverse effect limit (LOAEL), and the reference dose (RfD) (WHO, 2009). A NOAEL is the highest observable exposure level in which there were no statistically significant increases in the severity or frequency of adverse health effects (Alexeeff et al. 2001). However, these

values are subjected to a substantial degree of error from undetected incidences due to the small number of animals typically used in experiments which could contribute to significantly higher or lower effect up to 20% from the true dose-response level (Gaylor, 1992; Leisenring, 1992). In absence of a NOAEL, the NOAEL can be estimated from the LOAEL using the following equation:

Equation 2: NOAEL Estimation Equation (Alexeeff, 2001)

$$\text{NOAEL} = \frac{\text{LOAEL}}{\text{Uncertainty Factor}}$$

The uncertainty factor can range from 1 to 10 to account for greater health risk potentials but an uncertainty factor of 10 is the standard (USEPA, 1994). In instances where the extrapolation appears to be less than 10, lower uncertainty factors have been used; however, these instances lack justification for the lower uncertainty factors (Alexeeff, 2001). From the NOAEL, a reference dose can be extrapolated, again by applying an uncertainty factor (UF) and modifying factors (MF) (Equation 3):

Equation 3: RfD Estimation Equation (USEPA, 1993)

$$\text{RfD} = \frac{\text{NOAEL}}{\text{UF X MF}}$$

The RfD is an estimate of the daily exposure that is likely to have no observable effects over a lifetime and is used to gauge the potential effect of a chemical based on other doses (USEPA, 1993). The dose-response curve can also be utilized to develop a benchmark dose (BMD) which is means to approximate (USEPA, 2012). BMDs are commuted through statistical modelling of dose-response data to derive the most accurate dose at different confidence intervals (USEPA, 2012). Although methodology to calculate BMDs has existed for many years, BMD has yet to replace NOAEL and LOAEL within dose-response analysis despite being a more accurate calculation (Kodell, 2009).

Risk Characterization

The final step of risk assessment is risk characterization which is the qualitative and quantitative determination of the possibility of a hazard causing an adverse health effect with the inclusion of uncertainty factors (IPCS, 2004). This step integrates the intake and exposure assessments and the

hazard characterization to provide valuable data for risk management and decision-making (WHO, 2009). As part of the integration, risk characteristic incorporates uncertainty factors mainly through exposure estimates (EFSA 2005). However, a formal uncertainty analysis is not always necessary because the uncertainties are relatively small, and the risk characterization is often used for decision-making for which this risk analysis process is assumed to be either the most likely or the worst-case scenarios (WHO, 2009). Under these circumstances, a well-defined uncertainty analysis does not add valuable input to the decision-making process. As part of the risk characterization process, recommended exposure levels are often defined (WHO, 2009). These levels vary from organization to organization.

Exposure Levels

The EPA utilizes risk characterization data to develop their maximum contaminate level goals (MCLG) (Orme 1988). The MCLG is an aspirational goal based off the determination of an acceptable level of risk for a chemical. For known or probable carcinogens, there is no threshold level that is acceptable and therefore, the MCLG is set at zero (Orme 1988). For chemicals that are not known or probable carcinogens, the MCLG is determined utilizing available toxicity data and the human health concern from exposure to chemicals in drinking water. The first step in calculating the MCLG is to determine a reference dose. Once a reference dose has been calculated, the exposure is determined by the following equation:

Equation 4: Exposure Level (USEPA, 1988)

$$\text{Drinking water equivalent level (DWEL)} = \frac{\text{RfD} * \text{Bodyweight(kg)}}{\text{Drinking water consumption } (\frac{\text{L}}{\text{day}})}$$

The DWEL is them multiplied by the drinking water contribution to the exposure of a chemical to determine the MCLG. The EPA then utilizes the MCLG to determine their maximum contaminant level (MCL) which is an enforceable standard (Orme, 1988). The MCL set to be as close to the MCLG as feasible utilizing the best technology available and the cost of implementing that technology.

The Center for Disease Control's Agency for Toxic Substances and Disease Registry (ATSDR) has a similar exposure level based on the risk characterization. The ATSDR publishes a minimal risk level (MRL) which are an estimated daily exposure which are likely to not have adverse health effects during specified time durations of exposure (ATSDR 2005). Further, MRLs are not an enforceable standard, but a guideline for evaluating exposure and decision-making. The ATSDR calculates MRLs using the following equation:

Equation 5: MRL Equation (ATSDR, 2005)

$$\text{MRL} = \frac{\text{NOAEL}}{\text{Uncertainty Factors}}$$

This equation is identical to the EPA's reference dose calculation only the ATSDR and the EPA apply different uncertainty factors based on different circumstances. The ATSDR further calculates an environmental media evaluation guides (EMEG) for hazardous chemicals utilizing the following equation:

Equation 6: ATSDR EMEG Equation (ATSDR, 2005)

$$\text{EMEG} = \frac{\text{MRL} * \text{Bodyweigh(kg)}}{\text{Ingestion Rate } (\frac{\text{L}}{\text{Day}})}$$

Again, similarities between the EPA's DWEL and the ATSDR's EMEG are evident; however, the two exposure level calculations will yield significantly different results based on the agency's uncertainty factors.

A final example of exposure levels can be seen from the US Department of Health and Human Services National Toxicology Program (NTP). The NTP's Office of Health Assessment and Translation conducts a systematic review of a chemical to determine the probability of health effects (NTP, 2016). This process begins by developing population, exposure, comparators, and outcome (PECO) statements to aid in the search for data and research. Utilizing the PECO statements, a collection of studies in both animals and humans, both in vitro and in vivo are collected (NTP, 2016). These studies determine the

confidence rating in the collected body of evidence based on bias and associated outcomes. The evidence and confidence in the evidence are then used to determine the health effect conclusions (NTP, 2016). The level of evidence for health effects shown in human and animal studies are ranked as high, medium, or low, and then the chemical is categorized as a known, presumed, suspected, or not classifiable hazard based on Figure 6:

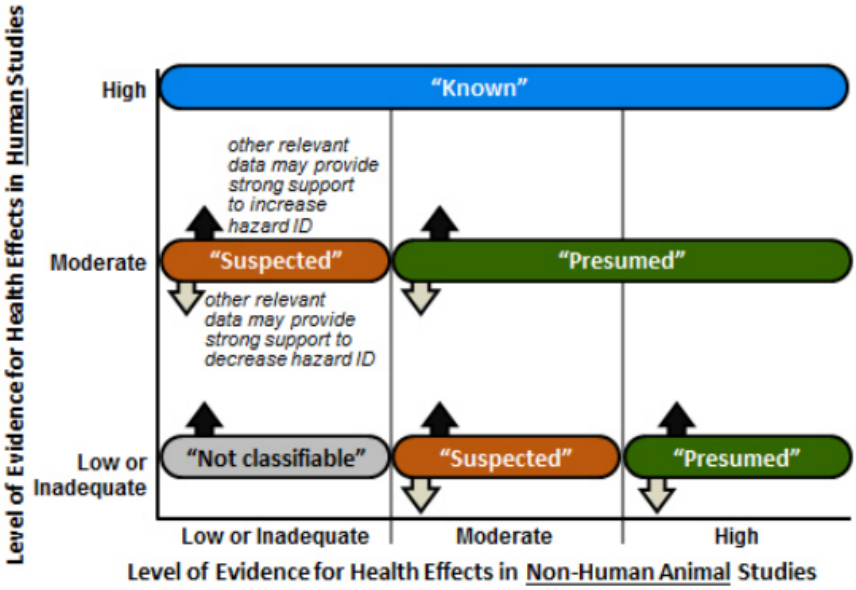


Figure 6: Hazard Identification Scheme (NTP, 2016)

Acceptable Risk

A level of risk can be characterized and determined based on the risk assessment process outlined previously; however, that process does not consider public perception. Determining risk has an inherent tie with public perception of risk and that perception should be considered when developing a risk assessment by determine what risk is acceptable (Hunter, 2001). There is no standard for defining acceptable or tolerable risk. One such method is arbitrarily defining probabilities of risk (Hunter, 2001).

This process is widely accepted in environmental regulation with a one in a million chance of developing cancer due to exposure to a chemical is viewed as essentially zero (WHO, 2009). The Food and Drug Administration determined that one chance in 100 million of developing cancer was deemed as safe until the reduced their limit to one in a million in 1977 (Cardon, 1994). The EPA uses a range from 10^{-4} to 10^{-6} for carcinogens as acceptable (Cotruvo 1988). Other organizations such as the United Kingdom's Health and Safety Executive uses a range for acceptable risk from one in 1000 deemed tolerable to one in a million deemed acceptable (RCEP, 1998).

Another approach to acceptable risk is setting the level at the level that is currently tolerated (Hunter, 2001). This approach assumes that whatever level of risk that the public is tolerating is acceptable to maintain. The EPA has utilized this method to set the allowable bacterial levels for bathing water based on what levels the public tolerated (USEPA, 1986). If the public is informed of the hazard and circumstances and still choose to tolerate the risk, this method could be a promising means of determining risk; however, this approach is significantly impacted by location and culture (Hunter, 2001).

Similar to the currently tolerated approach, acceptable risk could be based on epidemiological data in a disease burden approach (Hunter, 2001). By analyzing the current disease burden produced by the exposure to a chemical, acceptable risk could be set so that the disease burden does not exceed the current level. Although this approach may be useful for determining priorities, diseases are rarely attributed to a single chemical and therefore this approach would not fully capture the acceptable risk (Hunter and Fewtrell 2001). Reducing the disease burden of one route may not produce an overall reduction of the disease burden in the populations due to other sources of exposure being present (Hunter and Fewtrell 2001).

Another common approach to determining acceptable risk is with a cost-benefit analysis (Sloman, 1994). Although this may be a straight-forward approach, there are several limitations to defining acceptable risk based on the cost-benefit analysis. First, the exact number of cases of a disease may not be known with any certainty and the cost of the disease may be difficult to analyze (Hunter, 2001). One technique to overcome the issue with assigning cost to a disease is to use Quality Adjusted Life Years (QALYs) to determine acceptable risk (McCrone 1998). QALYs combine utility, length of life, and quality of life into one category which can be converted into a monetary value and therefore used to perform a cost-benefit analysis (Trusts 1992).

Ecological Risk Assessment

The final aspect that is incorporated into risk characterization is ecological risk determination which analyzes the probability that exposure to a chemical will impact the environment (US EPA). Unlike the process detailed above for human health assessment, ecological risk assessments do not have a standard methodology (US EPA n.d.). This is main due to the complexity associated with ecological risk. While human risk assessments are dealing with individuals, ecological risk can deal with individuals, populations, communities, or even ecosystems with each level becoming exponentially more complex than the previous (US EPA n.d.).

Risk Analysis of Per- and Polyfluoroalkyl Substances (PFAS)

High levels of PFOA and PFOS can be toxic for reproduction and development of fetuses and have shown some potential to be carcinogenic in animal tests (Lau et al., 2007; Fei et al., 2009; Joensen et al., 2009; Anderson et al., 2008). An epidemiological study of 69,000 people displayed potential links between PFOA and PFOS exposure and high cholesterol, ulcerative colitis, thyroid diseases, testicular cancer, kidney cancer, preeclampsia, and elevated blood pressure during pregnancy (Knox et al., 2011;

Frisbee et al., 2009; Lopez-Espinosa et al., 2011). This study was part of a class action settlement of a lawsuit against DuPont's Washington Works around which inhabitants showed blood concentrations of PFOA 500-times greater than the general population (OECD, 2013). The NTP also published a report of their risk characterization of PFOA and PFOS with both labeled as a presumed immune system hazard to humans with a high confidence from animal tests and a moderate confidence in human studies (NTP, 2016). The ATSDR also has a draft for public comment for perfluoroalkyls that lists the following MRLs for Oral Exposure:

Table 3: MRL for PFAS (Adapted from ATSDR, 2018)

Compound	MRL (mg/kg/day)	Effect	Point of Departure (mg/kg/day)	Uncertainty Factor
PFOA	$3x10^{-6}$	Neurodevelopmental	0.000821 (LOAEL)	300
PFOS	$2x10^{-6}$	Delayed eye opening	0.000515 (NOAEL)	30
		Decrease pup weight in rats		10

The U.S. EPA also released health advisories for both PFOA and PFOS at 70 parts per trillion, but the agencies has not released MCLs or MCLGs for these compounds (USEPA, 2016). Although most studies and limits have been implemented in recent years, PFAS have been in use for more than 60 years and a chronological progression of the publically perceived health risks has evolved since the start of production (Table 4).

Table 4: Evolution of Public Perception of PFAS Risk (Adapted from Grandjean and Clapp, 2014)

Year	Event
1947	PFC production starts at 3M plant in Cottage Grove, Minnesota
1956	PFC waste deposited from 3M plant

1962	Internal DuPont document raises concern about health risks of PFC
1970s	PFC vapor pressure and water solubilities are published
1978	Animal testing (monkeys) reveals immunotoxicity and other adverse health effects
1981	Concerns rise for birth defects in children of female production workers
1987	PFOA carcinogenicity reported from animal testing (rats)
1993	3M beings monitoring PFOA in serum of production workers
	Mortality study shows excessive occurrence of prostate cancer
1998	Serum from U.S. blood donors contains PFCs
2000	Persistence and global environmental dissemination of PFC observed
	3M announces plans to phase out PFOS
2002	3M PFOS phase-out completed
2008	Drinking water health risk limits for PFCs issued
	Animal testing (mice) shows immunotoxicity at serums concentrations similar to human exposure
2010	PFOA emissions decrease by 95%
2011	Animal testing (mice) shows low exposures induce delayed mammary gland development
2012	PFC immunotoxicity is reported in children

Public perception of PFAS contamination has shaped the risk assessments (Table 4). The Canadian Department of Veterinary Biomedical Sciences and Toxicology Centre compiled the results a several studies of ecotoxicology of PFAS with a focus on PFOS due to PFOS being the most common PFAS in environmental samples (Kannan, 2001). Giesy (2001) found that there was no evidence of acute toxicity in microorganisms in sewage nor acute toxicity in the aquatic macrophytes, *Lemna gibba.* Correlation have been found between the concentration of PFOS and developmental effects such as improper gut coiling, edema, and facial abnormalities in African-clawed frogs during acute exposure (Palmer, SJ, Krueger 2001; Giesy et al. n.d.). Further studies in fathead minnows showed adverse health

effects of erratic swimming during acute exposure at concentration greater than 5.6 mg/L of PFOS (Drottar, 2000). When aquatic organisms were exposed to chronic levels of PFOS, microorganisms still showed no evidence of toxicity, macrophytes had observable toxicity at concentrations greater than 3 mg/L of PFOS, amphibians showed no significant effects at concentrations less than 1.0 mg/L, and fish had no sign of effect at concentrations less than 0.3 mg/L (Giesy et al. 2010). Giesy (2001) found little evidence of an ecotoxicological effect of PFAS in aquatic organisms.

Life Cycle Impact Assessment of Treatment Techniques

Although GAC, IEX and supplying bottle water to exposed populations are viable options for counteracting PFAS contamination, each of these treatment techniques has an associated life cycle impact to human health (Emery et al., 2019). GAC and IEX treatments require large amounts of energy consumption both for operation of the treatment system as well as for the incineration of the used GAC (Bayer and Finkel, 2006; Jeswani et al., 2015; Isla-cabaraban et al, 2016). These energy costs are typically supplied using energy derived from coal which releases additional contaminants into the air and the water (Emery et al., 2019). Supplying bottled water has an associated human health impact that is dominated by the production of the plastic for the bottles for locally sourced bottled water or transport impacts for long-distance shipping (Gleick and Cooley, 2009). Emery et al. developed life cycle impact assessments for GAC, IEX, and supplying bottled water for varying concentrations of PFAs contaminations (Figure 7).

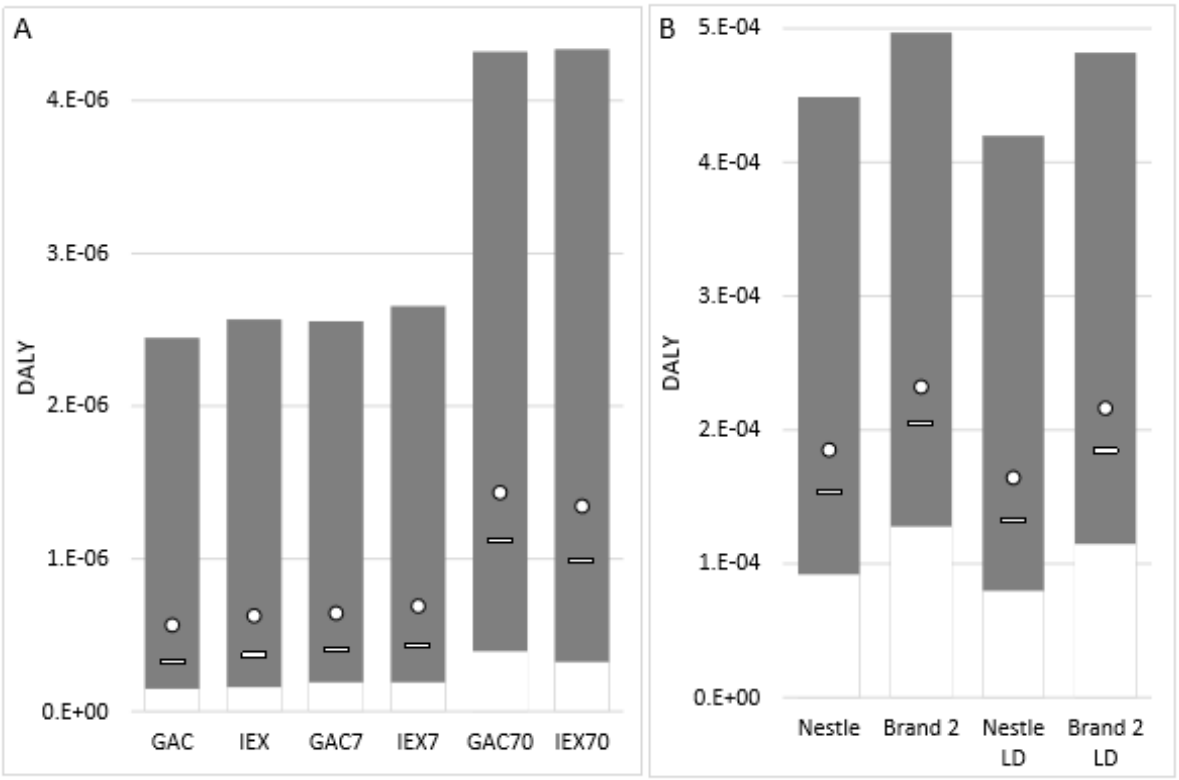


Figure 7: Human health impacts of treatment technologies for contaminant concentrations of 0.7, 7.0, and 70 ug/L and (B) human health impact of supplying bottled water with resident pick-up or delivery. (Emery et al., 2019) ▭ *median* ○ *mean*

Human health impacts of treatment technologies expose a knowledge gap in PFAS treatment and remediation in that there is no comparison of these life cycle impacts of treatment technologies to the human health impact of the PFAS contamination.

III. Methodology

This chapter discussed the methodology used to investigate and answer the research questions posed for this research effort. This section identifies the models, sources, and procedures used to perform this research.

USEtox®

A scientific toxicological model was needed in for the base of the toxicological risk assessment of the selected PFAS compounds. USEtox is a scientific consensus model that characterizes human and ecotoxicological impacts of various chemicals; however, their database does not have a toxicological risk assessment available for PFAS. The USEtox model was used as the base of the toxicological model developed in this research because USEtox is endorsed by the United Nations Environment Program's Society of Environmental Toxicology and Chemistry Life Cycle Initiative and was capable of being modified for the PFAS data available.

The USEtox model produces a life cycle impact assessment through the summation of pollutants released by a system using the following equation:

Equation 7: Impact Score Equation

$$IS = \sum\sum CF * M$$

Where IS is the impact score for the toxicity of a compound in the unit of cases of adverse health effect, CF is the characterization factor of a chemical released in units of cases per kg, and M is the amount of the chemical emitted in kg. The characterization factor units are equated to Comparative Toxic Units (CTU).

The characterization factor requires three factors to be complete: effect factor (EF), exposure factor (XF), and fate factor (FF). The characterization factors for the potential increase of adverse health effects in Comparable Toxic Units (CTU) were calculated using the following equation:

Equation 8: Characterization Factor

$$CF = EF * XF * FF$$

The effect factor for human toxicity is calculated using the following equation:

Equation 9: Effect Factor

$$EF = \frac{0.5}{ED50}$$

Where the ED50 is effective dose at which 50% of the population will experience the adverse health effect. This assumes linearity between concentration and response up to the 50% point. The ED50 was calculated using the following equation:

Equation 10: Human Expected Dose at which 50% of the Population will Experience Adverse Health Effects

$$ED50 = \frac{ED50_a * BW * LT * N}{AF_a * AF_t * 10^6}$$

Where $ED50_a$ is the daily dose exposed during animal testing in which there was a 50% probability of a disease, AF_a is the extrapolation factor for interspecies differences (see Table 1), AF_t is the extrapolation factor for differences in time of exposure, BW is the average body weight of a human, LT is the average lifetime of a human, and N is the number of days per year. The AF_t used for this research was the USETox recommended factor of 5 to extrapolate from subacute to chronic exposure (Huijbregts et al., 2005). The body weight and lifetime used came from the EPA recommended values, 70kg and 70 years respectively (EPA 2016).

Table 5: Interspecies extrapolation factors (Huijbregts et al., 2005)

Type	$AF_{interspecies}$ (-)	Average Bodyweight (kg)
Human	1.0	70
Monkey	1.9	5
Rabbit	2.4	2
Rat	4.1	0.250
Mouse	7.3	0.025

The $ED50_a$ was calculated using the following equation:

Equation 11: Animal Expected Dose at which 50% of the Population Experiences Adverse Health Effects

$$ED50_a = NOAEL * AF_N$$

Where NOAEL (no-observed adverse effect level) is the daily dose per body weight that causes no adverse health effects during an animal testing and AF_N is an extrapolation factor from NOAEL to ED50. The AF_N used for this research was the USETox recommended 9 (Huijbregts et al, 2005).

For any data compiled that did not have a reported NOAEL, a conversion from the LOAEL (lowest observed adverse effect level) was utilized:

Equation 12: NOAEL Conversion from LOAEL

$$NOAEL = \frac{LOAEL}{AF_L}$$

Where LOAEL is the reported lowest observed adverse effect level from animal testing and AF_L is an extrapolation factor. An AF_L of 4 was used for this research in accordance with the USETox user guidelines (Huijbregts et al., 2005).

The fate factor and the exposure factors can be combined to make the intake fraction representing how much of a chemical enters the human population using the following equation:

Equation 13: Intake Fraction

$$iF = FF * XF$$

Due to limited research in the toxicology of PFAS, the fate factor and exposure factor were not able to be modeled in the USEtox software and therefore were modified to fit the data available. Since only the current PFAS contamination and the concentration in the soil and drinking water can be determined at Air Force bases, the fate factor and exposure factors were modified to use a range of concentrations in order to develop the toxicity model. Since the intake fraction is the amount of a chemical exposed to the population compared to what is released, these terms can be replaced utilizing the following equation:

Equation 14: Modified Intake Fraction

$$iF = C * Ing * X * Pop$$

Where C is the known or expected concentrations of PFAS, Ing is the amount of water ingested per person per day, X is the exposure factor of these concentrations, and Pop is the population being exposure. For this research, concentration ranges from 7 parts per trillion to 70 parts per billion were used to cover the existing released from public agencies as well to compare this research to that of previous PFAS treatment research. The ingestion factor was assumed to be 1.2 L/person/day based off EPA average drinking water consumption (EPA 2018). The elimination factor of 5% of PFOA and 25% of PFOS is eliminated from the body before being absorb (Ying et al., 2013). The population used for this research was the population of the resident on Wright-Patterson AFB which is estimated to be 2000 people (US Census Bureau, 2010).

Data Collection:

The animal testing data was collected from the same sources utilized by the ATSDR's PFAS draft toxicological profile (ATSDR, 2018). This data was selected in order to have the most comparable data to public agency's publications. This data was collected, analyzed and converted into the toxicology modeling. After this data was compiled, the data was reviewed for accuracy and reliability. Three data points were removed due being four orders of magnitude lower LOAEL than the remaining data. These points were all performed by the same animal test, testing for a specific endocrine disruption. Due to these tests focusing on such a specific impact and falling significantly outside the remaining data, these points were omitted. The data collected for PFOA and PFOS resulted in distribution ranges for varying adverse health effects; however, the short chain and other alternatives did not yield enough data for analysis of various adverse health effects.

Monte Carlo:

Once the PFOA and PFOS data was compiled and modeling conducted using the modified USEtox process, a Monte Carlo simulation was utilized to determine the distribution for the effect factor based on the distributions of the varying adverse health effects. A Monte Carlo simulation was utilized due to the deterministic result gained from using randomly selected samples from the data to develop the characterization factors for PFOA and PFOS. Monte Carlo simulations were performed assuming the effect factor distribution would be a normal distribution which is the standard assumption of Monte Carlo simulations. However, simulations for a resulting log-normal scale were performed based on similar analysis from another life cycle impact assessment modeling software, SimaPro (Goedkoop, 2016).

The Monte Carlo simulations were performed for PFOA and PFOS individually as well as a combined effect of PFOA and PFOS. A combined simulation was run due to the EPA Health Advisory using a

combined concentration of PFOA and PFOS (EPA, 2016). This also aligns with the research that shows that treatment for PFOA and PFOS is similar and a GAC or IEX treatment would remediate both compounds in a similar procedure (ATSDR, 2018).

The short chain and alternatives (PFBS, PFHxS, PFBA, PFHxA, and 6:2FTOH) did not have enough data to make Monte Carlo simulations a viable option. These chemicals were run through the modified USEtox model with the data available to develop a single characterization factor value that was used for analysis.

This analysis developed the effect factors for the various compounds from which the characterization factors were modeled using the methodology discussed in Methodology Section 1.1: USEtox®.

Analysis:

Analyses were performed on the data for PFOA and PFOS to determine if a difference existed between adverse health effects, animal species, and gender. For these analyses, an analysis of variance (ANOVA) was performed. ANOVA was selected as an analysis test to determine if the means between groups had a significant variance with a p-value less than an alpha of 0.05. This analysis was continued, using a Tukey Test to determine the cause of any statistically significant differences. A Tukey test compares the means of the different categories to all other means other the other categories. For example, when the Tukey test compared the mean of a systemic adverse health effect to the means of all other health effects then continued through all adverse health effects until every mean had been compared to all other means of adverse health effect.

Scenarios Assessed:

This research model the toxicological life cycle assessment of PFOA, PFOS, PFBS, PFHxS, PFBA, PFHxA, and 6:2FTOH in order to compare these chemicals to each other and to the life cycle impact assessments of granulated activated carbon (GAC) and Ion-exchange (IEX) treatment techniques. Due to the availability of data for PFOA and PFOS, the results from the Monte Carlo simulations were utilized for the comparison to the other chemicals and the treatment techniques. The results were compared to the findings by Emery's *Evaluation of Treatment Options for Potable Water Impacted with Perfluorinated Alkyl Substances Using Life Cycle Assessment*. This study found the following CTUs for remediating PFAS contamination using GAC, IEX, and distributing bottled water to vulnerable populations for various contamination concentrations:

Table 6: Toxicity results for supply of $1m^3$ remediated water (Emery et al., 2017)

	PFOA and PFOS Combined Concentration (*µg/L)*					
	0.7		7.0		70	
Impact Category	GAC	IEX	GAC	IEX	GAC	IEX
CTU	9.3E-08	9.6E-08	9.9E-08	9.7E-08	1.5E-08	1.1E-07

Table 7: Baseline results for supply of bottled water in CTU (Emery et al., 2017)

Scenario (CTU)			
Local Distribution		Bottle Water	
Brand 1	Brand 2	Brand 1	Brand 2
3.2E-05	4.4E-05	3.3E-05	4.5E-05

Comparison to Treatment Techniques:

With the data compiled and ran through the model, the results can be compared to the Emery's (2019) life cycle impact assessment of treatment techniques. This analysis was performed by comparing

the means of the treatment techniques to the means of the characterization factors. The means for all compounds were compared to the means for the three treatment options assuming a concentration of 0.7, 7.0, and 70 *µg/L.* The combined PFOA and PFOS was compared varying the concentrations of PFOA and PFOS by 0.1 *µg/L* so that the in-situ contamination values were equal to 0.7, 7.0 and 70 for comparing the values to the treatment techniques.

Linear Assessment:

Based on the treatment impact data available, CTUs for other concentrations could not be accurately extrapolated; however, assuming that the treatment CTUs would stay at the same level as the 0.7 *µg/L* values, a linear extrapolation was developed to identify the concentrations at which the treatment technique's impacts would likely exceed the impacts of the chemicals. This methodology can be used assuming that the two main contributing factors to the CTU for treatment where energy costs and transportation. For concentrations less than 7 *µg/L*, the energy costs to run the equipment and the transportation cost to transport the used materials would stay relatively equal because the GAC and IEX would be absorbing additional contaminated and particles in the water resulting in similar lifecycles of the materials used for remediation (MDH, 2010).

Assumptions and Uncertainty:

Throughout this study several assumptions have been made in order to maintain effective yet concise research. The assumptions using the adjustment factors regarding the effect factor were made to extrapolate animal testing data to human equivalence. These adjustment factors are a means to limit uncertainty but remain conservative estimates resulting in a higher effect factor. Assuming concentration can be substituted for fate and exposure is a worst-case scenario increasing the CTU value. Assuming linear impacts for treatments at concentrations less than 700 parts per trillion allows us to determine the treatment levels, but in doing so, the CTU impacts of treatment increase. This counteracts the assumption of substituting concentrations (Table 8).

Table 8: Uncertainty Table for assumptions throughout research

Assumption	Impacted Factor	Direction of Impact	Degree of Impact
Interspecies Adjustment Factor	Effect Factor	Increases	High
Time of Exposure Adjustment Factor	Effect Factor	Increases	Low
LOAEL to NOAEL Adjustment Factor	Effect Factor	Increases	Low
Linear Dose-Response	Effect Factor	Decreases extremes	Moderate
Substituting Concentration	PFAS Characterization Factor	Increases	Moderate
Linear Assessment of Treatment Impacts	Treatment Characterization Factor	Increases	Moderate
Publication Bias	All	Varies	Low

IV. Results and Discussion

This chapter presents the analysis of the results from the short and long chain toxicological impact model as well as the comparison to treatment technologies.

For analysis of the short chain PFAS toxicological impact models, due to lack of data, were analyzed using mean values of the comparative toxic units or single value points for PFAS with limited testing and data. These results are presented in values of CTUs for comparison between chemicals and treatment technologies.

Comparing treatment technologies to various PFAS compounds at a concentration of seven parts per trillion, the greatest impacts come from treatment (Figure 8). Emery (2019) did not model treatment impacts under 0.7µg/L (70 parts per trillion) so the treatment values were extrapolated under the assumption that at low concentrations of PFAS, other contaminants and particles in the influent water will be removed during the treatment resulting in similar overall adverse health impacts as the 70 parts per trillion (Shih, 2003). The results from this analysis show that the impact of treating PFAS exceeds the impact from the PFAS at concentrations of seven parts per trillion and below.

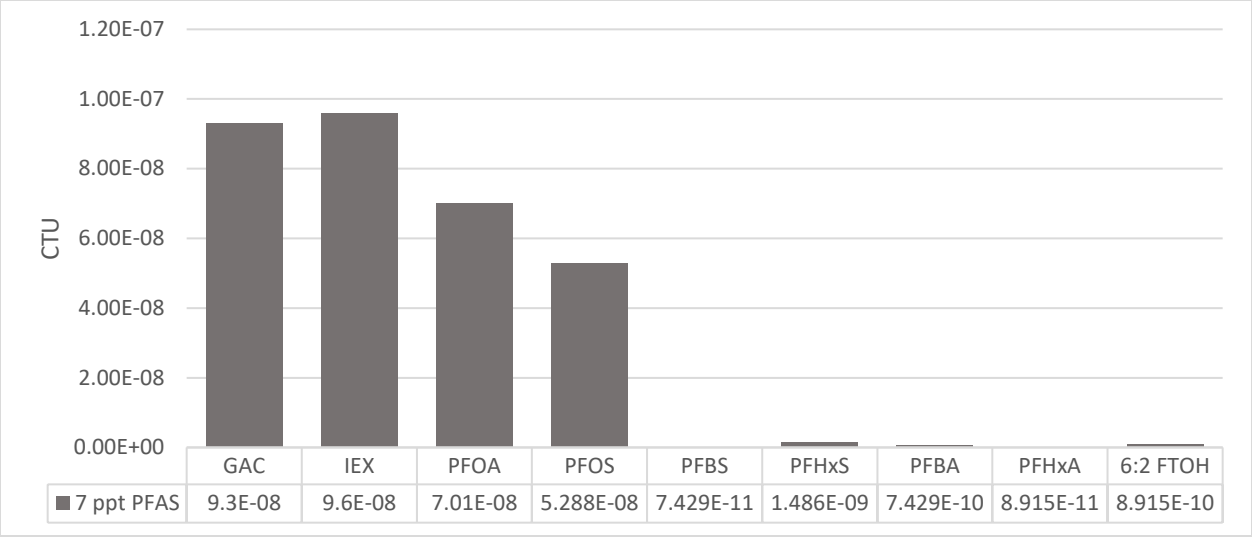


Figure 8: Comparison of CTU Values Using a Concentration of 7 ppt of PFAS

PFOA and PFOS were found to have adverse impacts that outweigh the impacts of treatment at concentrations as low as 70 parts per trillion (Figure 8-12). Comparing the results, at concentrations lower than 70 parts per trillion, treatment impacts fall below PFOA and PFOS impacts. This is significant due to the EPA's Lifetime Health Advisory which is set at 70 parts per trillion. Even below that limit, treating lesser contaminated drinking water will result in a less human toxicological benefits. The impacts of PFOA and PFOS at concentrations greater than 70 parts per trillion grow significantly far exceeding that of the treatment impacts (Figure 9 through Figure 12). PFOS and PFOA impacts are four orders of magnitude greater than the impacts of treatment technologies at concentrations of 70 parts per billion (Figure 12).

The Impacts of PFAS alternatives (PFBS, PFBHxS, PFBA, PFHxA, and 6:2 FTOH) fall orders of magnitude below PFOA and PFOS as well as below treatment technologies (Figure 8 and Figure 9). This shows that these alternatives, when exposed at similar concentrations, have a significantly lower impact on human health.

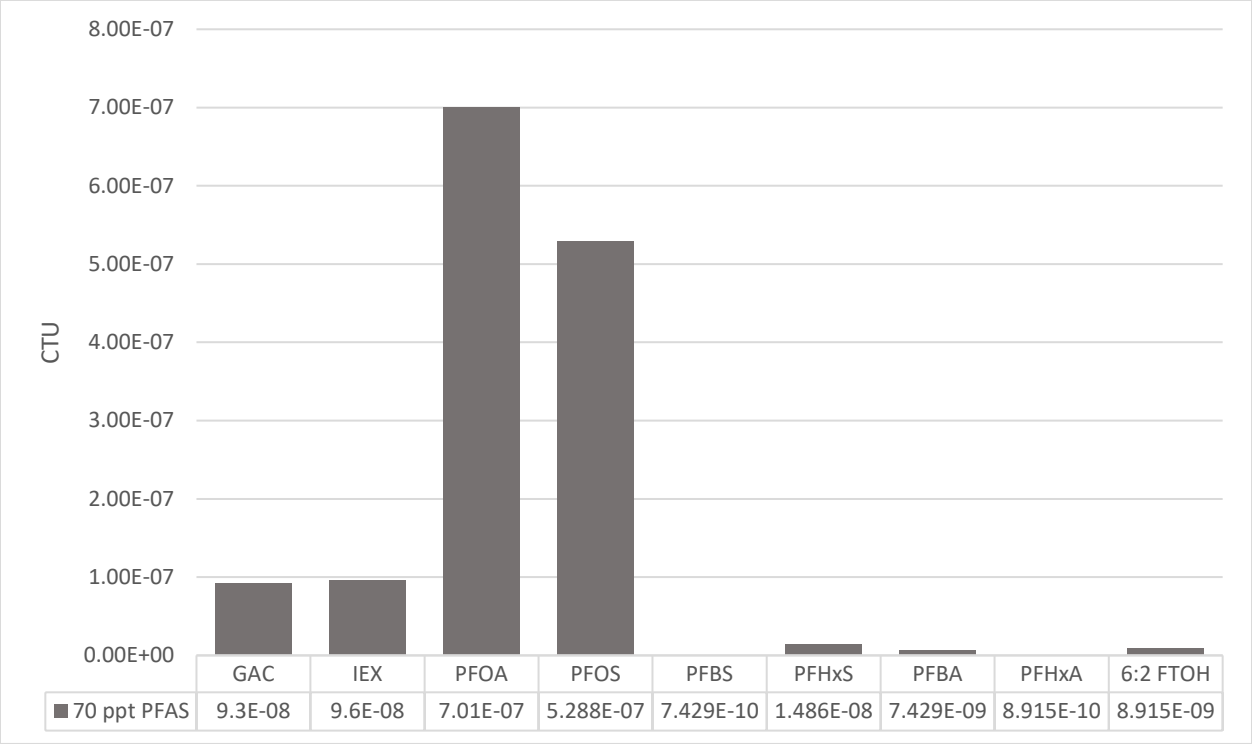


Figure 9: Comparison of CTU Values Using a Concentration of 70 ppt of PFAS

The concentrations at which treatment technologies begin to show favorability over the short chain and PFAS alternatives (Figure 10). The treatment technologies impacts at PFAS concentrations exceeding 700 parts per trillion are less than the impacts of the exposure to all PFAS compounds save PFHxA. PFHxA impacts do not exceed treatment technologies until concentrations of 70 parts per billion (Figure 12).

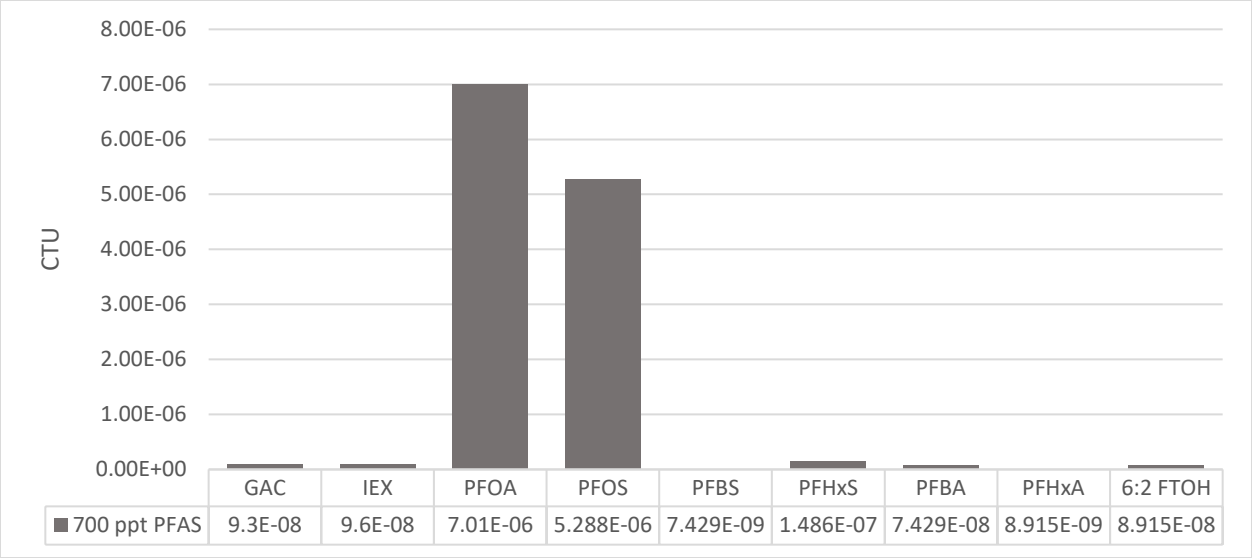


Figure 10: Comparison of CTU Values Using a Concentration of 700 ppt of PFAS

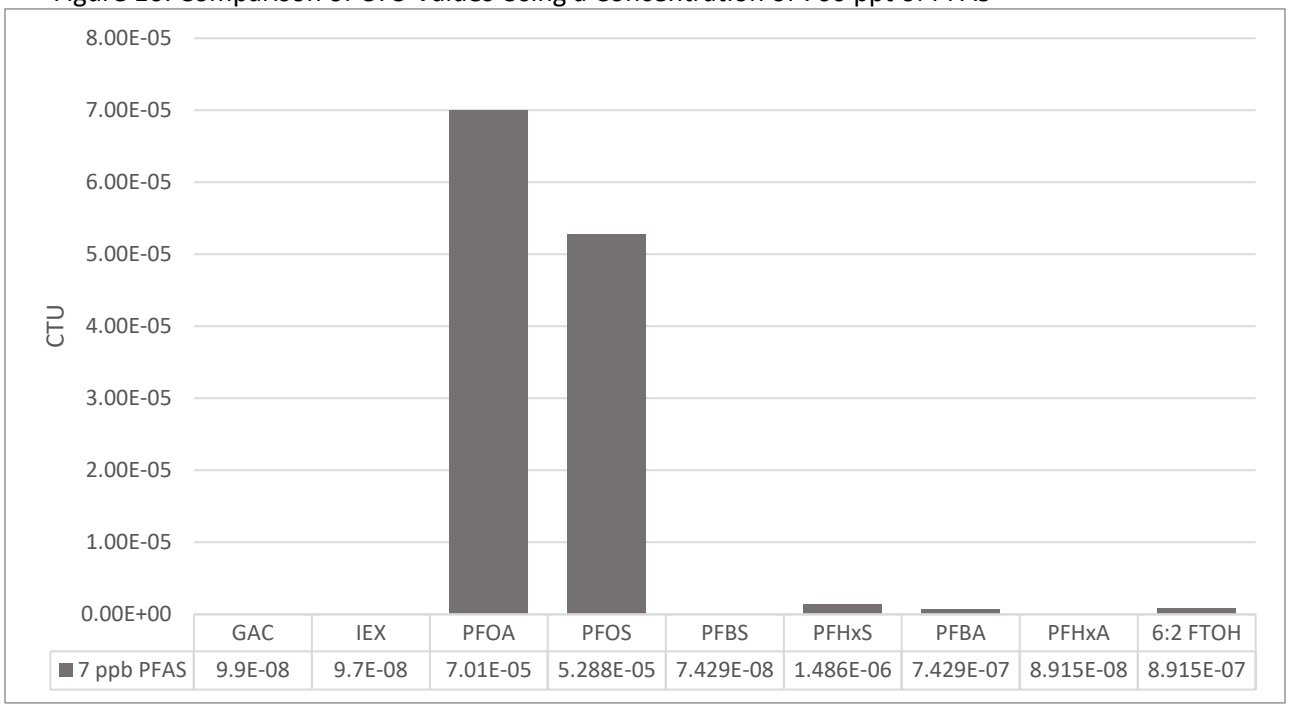


Figure 11: Comparison of CTU Values Using a Concentration of 7 ppb of PFAS

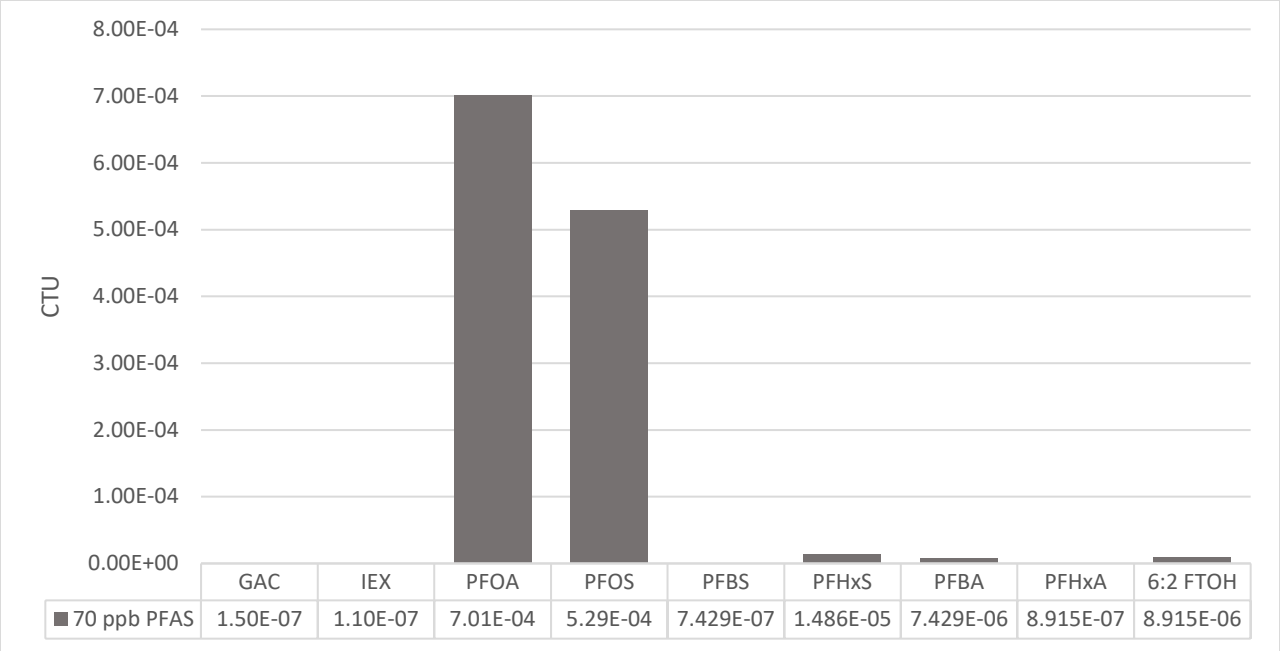


Figure 12: Comparison of CTU Values Using a Concentration of 70 ppb of PFAS

The change in CTU for treatment technologies across all concentrations analyzed (Figure 13). There is a steady rise of the treatment technologies versus the significant growth of PFAS impacts. Treatment technologies impacts do increase as concentration increases.

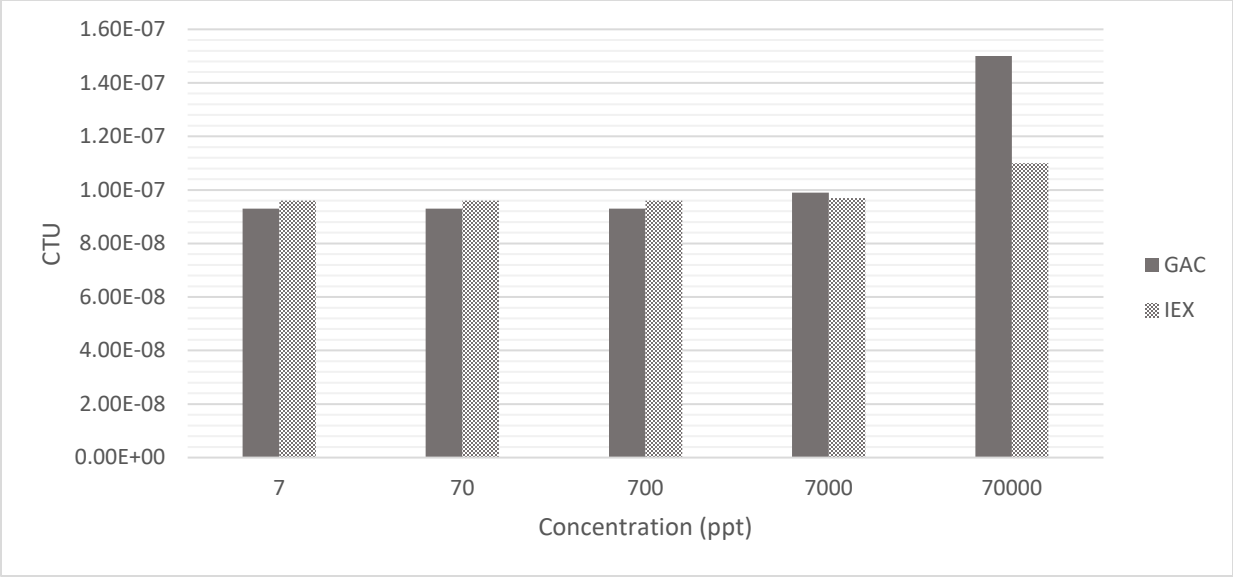


Figure 13: CTU Values for Treatment Technologies Across Varying Concentrations

. At concentrations below 700 parts per trillion, treatment impacts are assumed to become linear due to the treatment technologies inability to target PFAS compounds but rather eliminate any contaminants that might be present. From this analysis, the only applicable results are for treatment levels of PFOA and PFOS. From the preliminary results, the benefit of treating PFOA and PFOS contamination based on a human health impact are 10 and 13 ppt, respectively. When the assumed elimination rates are considered for contamination exposure, those treatment levels increase slightly to 11 and 17 parts per trillion for PFOA and PFOS respectively.

Table 9: Treatment Levels Assuming a Linear Treatment CTU at Concentrations under 700 ppt for Full Exposure and Exposure Assuming Elimination Rates of 5% for PFOA, 25% for PFOS, and 80% for Short Chain PFAS

Compound	Concentration when Treatment Outweighs Impact (ppt)	With Elimination Rates (ppt)
PFOA	10	11
PFOS	13	17

PFHxS	>700	>700
PFBS	>700	>700
PFBA	>700	>700
6:2 FTOH	>700	>700

Statistical Analysis Results:

After concluding the comparison to treatments, PFOA and PFOS data was analyzed to determine if there were any sources of statistical variation between species of animal, adverse health effect symptoms, and gender. Figure 14 shows the data ranges of PFOA data analyzed with box-and-whisker plots overlaid to better show the quartiles of the data. The Tukey-Kramer plot indicates the ranges of the data distributions. If circles are overlapping, they are assumed to be statistically equal. From this data we see that one of animal species researched has a statistically significant different in distribution.

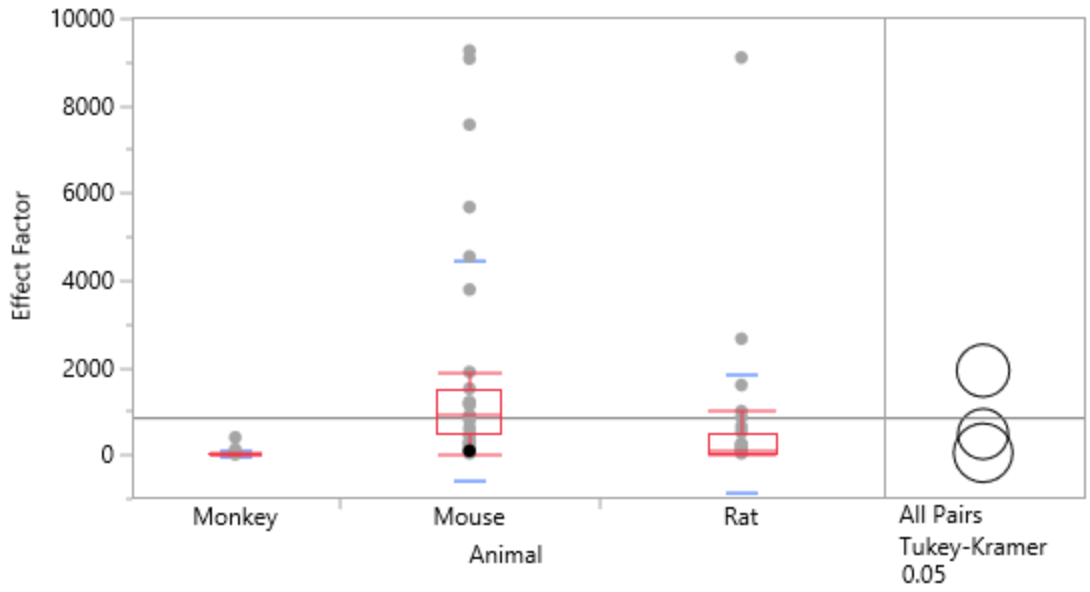


Figure 14: Analysis of Variances of PFOA Comparing the Distribution of Animal Species with Box-and-Whisker Plots showing the Quartiles found within the Data. The Circles for the Tukey-Kramer Plot Indicate the Acceptable Values of the Means Based on the Standard Deviations.

Figure 15 and Figure 16 show the results of further analysis into these data categories. There are statistically significant differences in animal species based on the variation of their distributions (Figure 15). With a F value falling below 0.05, or a 95% confidence interval, further analysis was performed to determine which species varied statistically. The results of the Tukey-Kramer test showing a statistically significant difference in the distributions with the mouse data distribution (Figure 16). Data collected from animal studies with mice had a statistically significant difference after the interspecies extrapolation factors had been applied.

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Animal	2	82521898	41260949	14.1916	<.0001*
Error	127	369242247	2907419.3		
C. Total	129	451764145			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Monkey	36	39.02	284.19	-523	601.4
Mouse	45	1921.70	254.18	1419	2424.7
Rat	49	467.70	243.59	-14	949.7

Std Error uses a pooled estimate of error variance

Figure 15: Results of ANOVA Testing on Various Animal Species from PFOA Data

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Mouse	Monkey	1882.680	381.2754	978.470	2786.890	<.0001*
Mouse	Rat	1453.999	352.0574	619.080	2288.917	0.0002*
Rat	Monkey	428.681	374.2950	-458.974	1316.337	0.4881

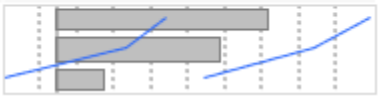


Figure 16: Results from Tukey-Kramer Analysis Showing Statistically Significant Differences in Distribution of Data Based on Animal Species

These analyzes continued for the PFOA data analyzing differences in gender and symptoms; however, there were no statistically significant results (Figure 17 and Figure 18). There was no difference found in the data between genders nor between the various adverse health effects analyzed. This contradicts our expectations that different symptoms would have larger impacts on the effect factors analyzed.

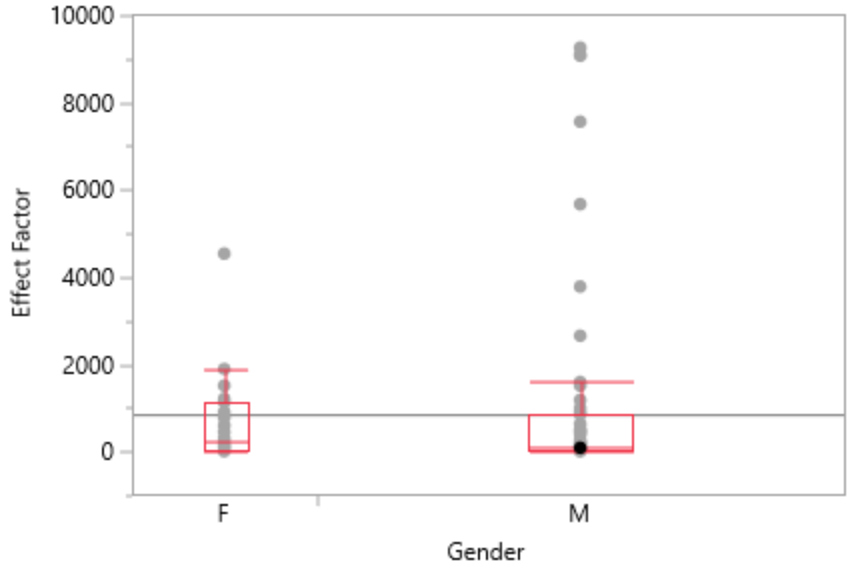


Figure 17: Analysis of Variances on the Effect of Gender on PFOA Effect Factor with Box-and-Whisker Overlays showing the different data quartiles

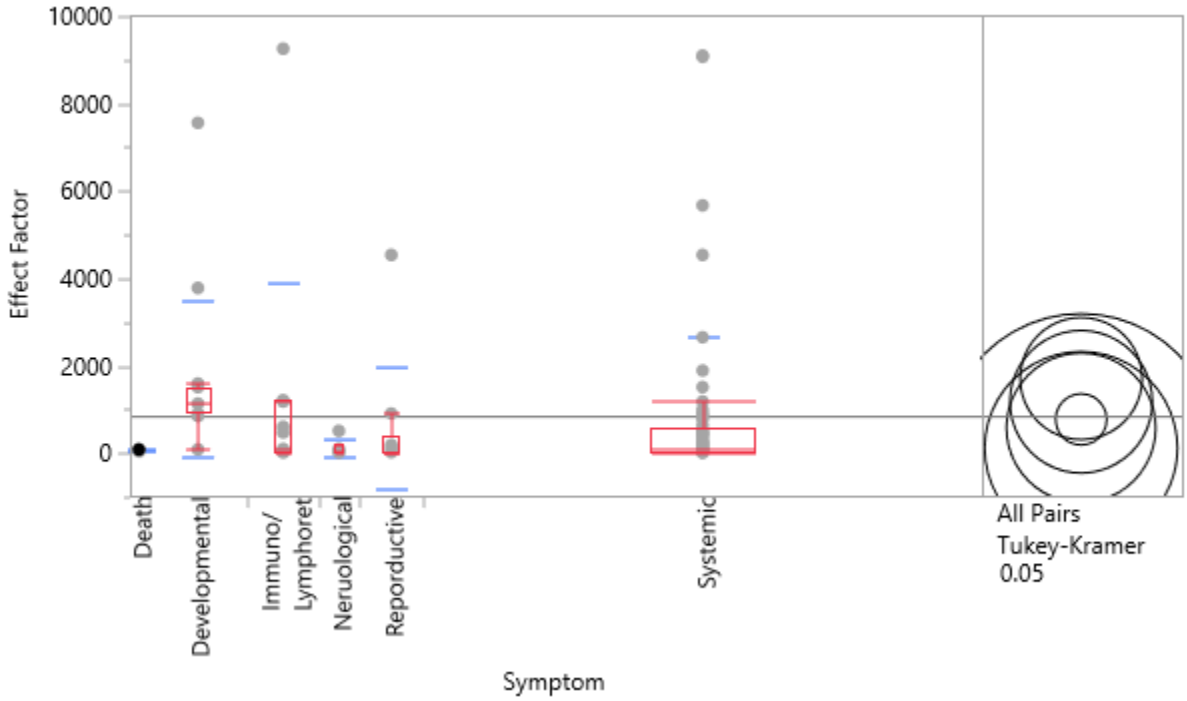


Figure 18: Analysis of Variances on the PFOA Effect of Symptom on Effect Factor with Box-and-Whisker Overlays showing the different data quartiles. The Circles for the Tukey-Kramer Plot Indicate the Acceptable Values of the Means Based on the Standard Deviations.

Similarly, the same analyses were performed on the data collected for PFOS effect factors giving the analysis of variance results (Figure 19 -21). These analyses showed no significant differences in any of the categories: symptoms, animal species, and gender. The analysis for animal species and gender garnered expected results in that there were no statistical differences between the different categories; however, again the results for symptoms was contrary to our expectations. This analysis showed that the PFOS data for the distributions of symptoms had no significant differences.

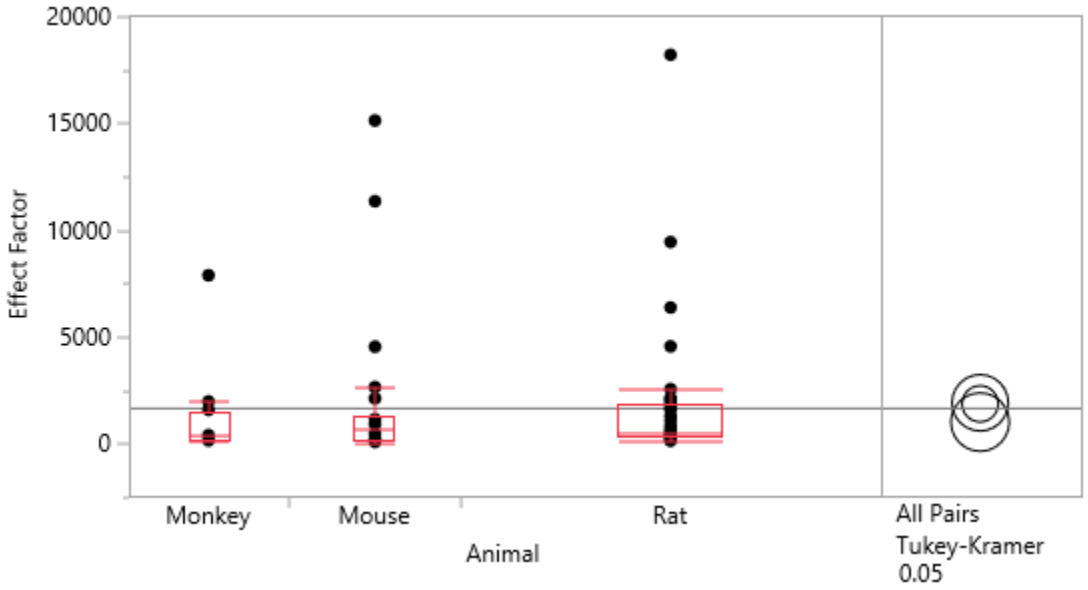


Figure 19: Statistical Analysis of PFOS Comparing the Distribution of Animal Species with Box-and-Whisker Plots showing the Quartiles found within the Data. The Circles for the Tukey-Kramer Plot Indicate the Acceptable Values of the Means Based on the Standard Deviations.

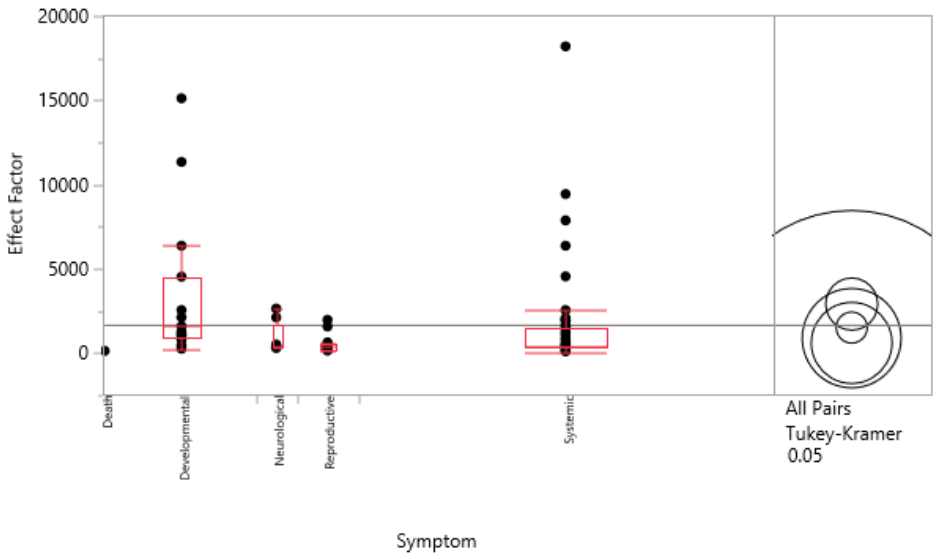


Figure 20: Statistical Analysis on the PFOS Effect of Symptom on Effect Factor with Box-and-Whisker Overlays showing the different data quartiles. The Circles for the Tukey-Kramer Plot Indicate the Acceptable Values of the Means Based on the Standard Deviations

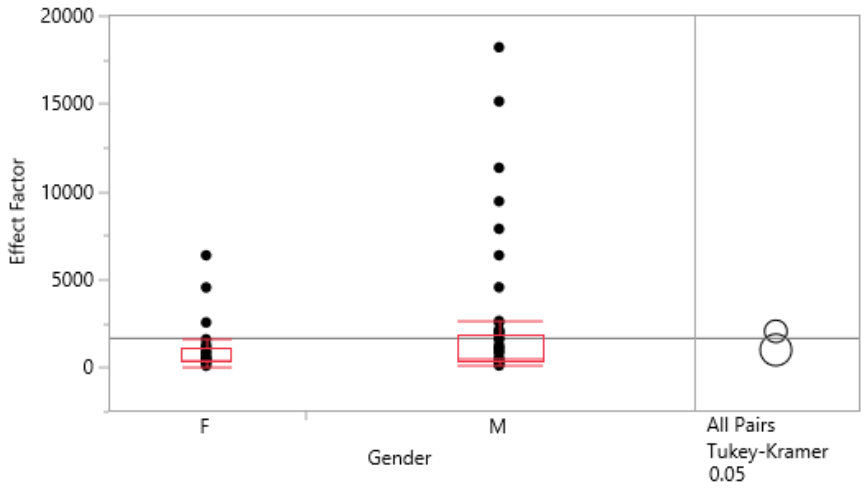


Figure 21: Box-and-Whisker plots of the effect of gender on PFOS Effect Factor

Figure 22 and Figure 23 show the result from the Monte Carlo simulation for PFOA with Figure 22 showing the results assuming a normal distribution and Figure 23 assuming a log-normal distribution.

The most notable result from these figures are the means of 9,329 and 5,937 respectively. These means are used to calculate the CTU for PFOA to compare to the treatment technologies.

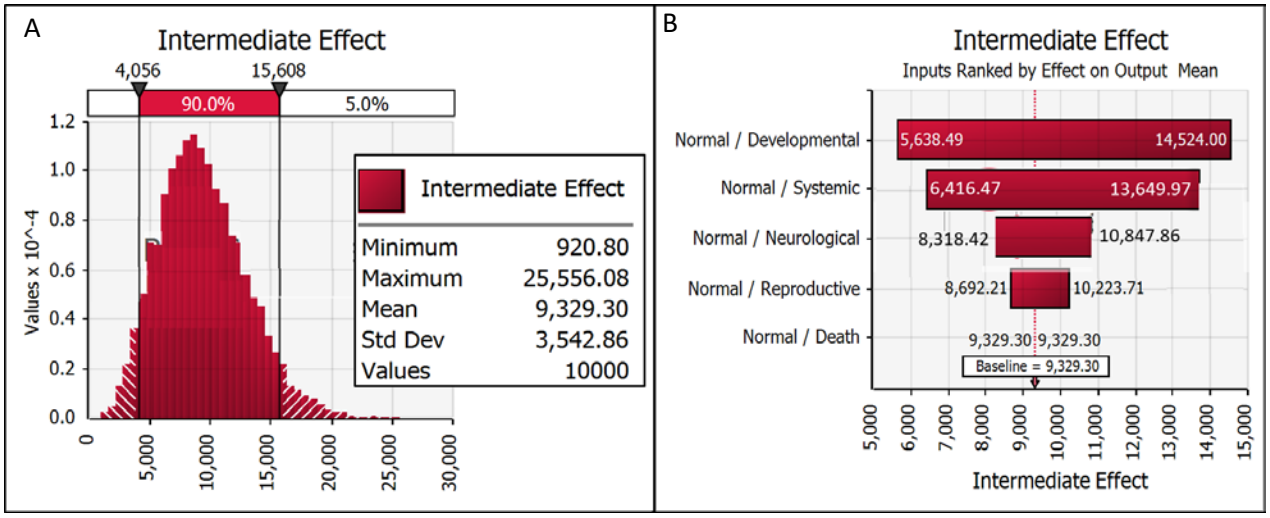


Figure 22: Monte Carlo Simulation Results for Intermediate Effect Factors of PFOA Using Varying Inputs of Symptom Distributions Assuming a Normal Distribution Result. A shows the normal distribution results for the simulation. B shows the tornado plot with data ranges for varying symptoms with maximum and minimum values displayed.

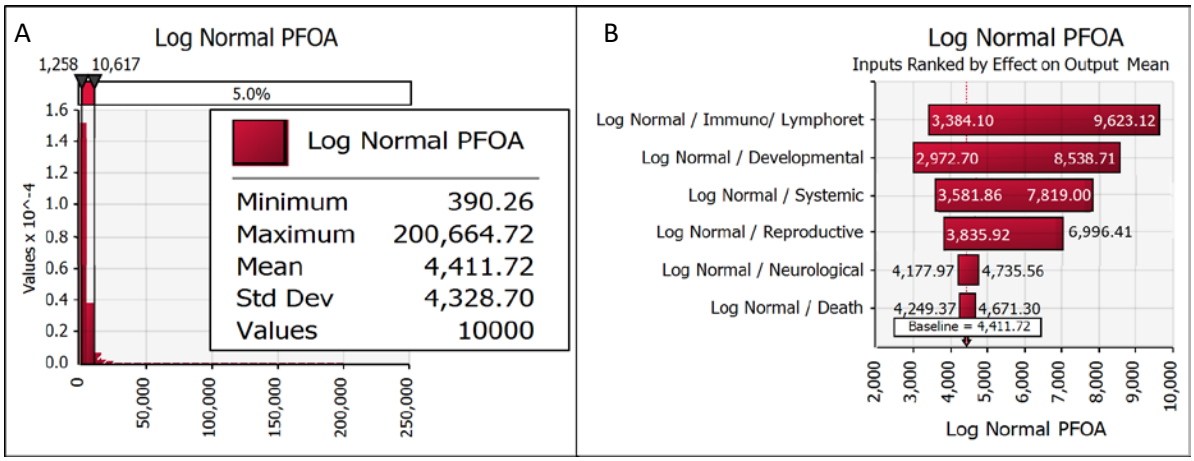


Figure 23: Monte Carlo Simulation Results for Intermediate Effect Factors of PFOA Using Varying Inputs of Symptom Distributions Assuming a Log-Normal Distribution Result. A shows the normal distribution results for the simulation. B shows the tornado plot with data ranges for varying symptoms with maximum and minimum values displayed.

Figure 24 and Figure 25 show the Monte Carlo results for PFOS assuming normal and log-normal distributions respectively. The means used for further analysis were 8,388 and 4,411 respectively.

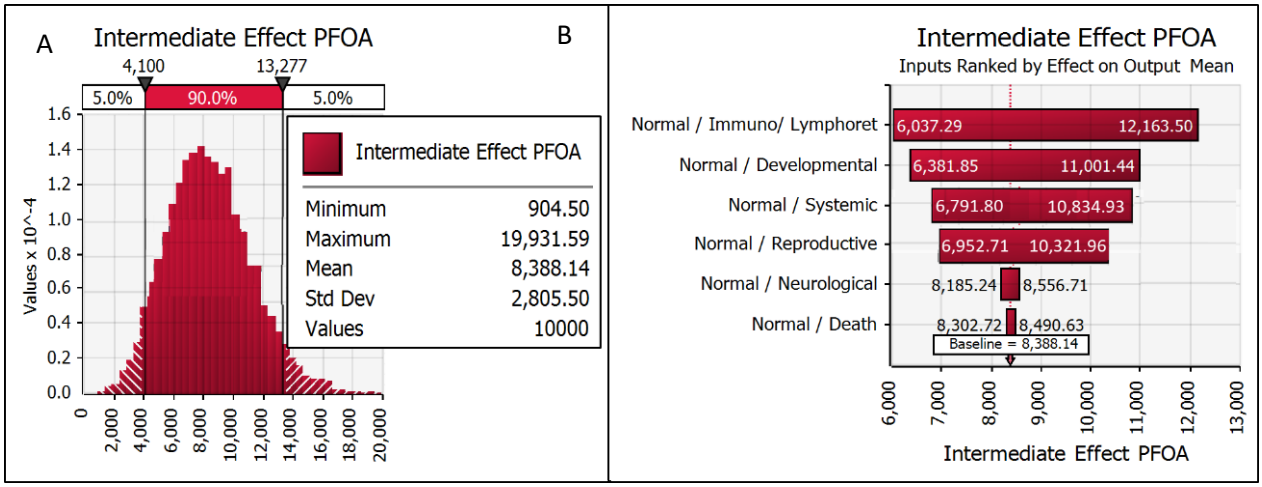


Figure 24: Monte Carlo Simulation Results for Intermediate Effect Factors of PFOA Using Varying Inputs of Symptom Distributions Assuming a Normal Distribution Result. A shows the normal distribution results for the simulation. B shows the tornado plot with data ranges for varying symptoms with maximum and minimum values displayed.

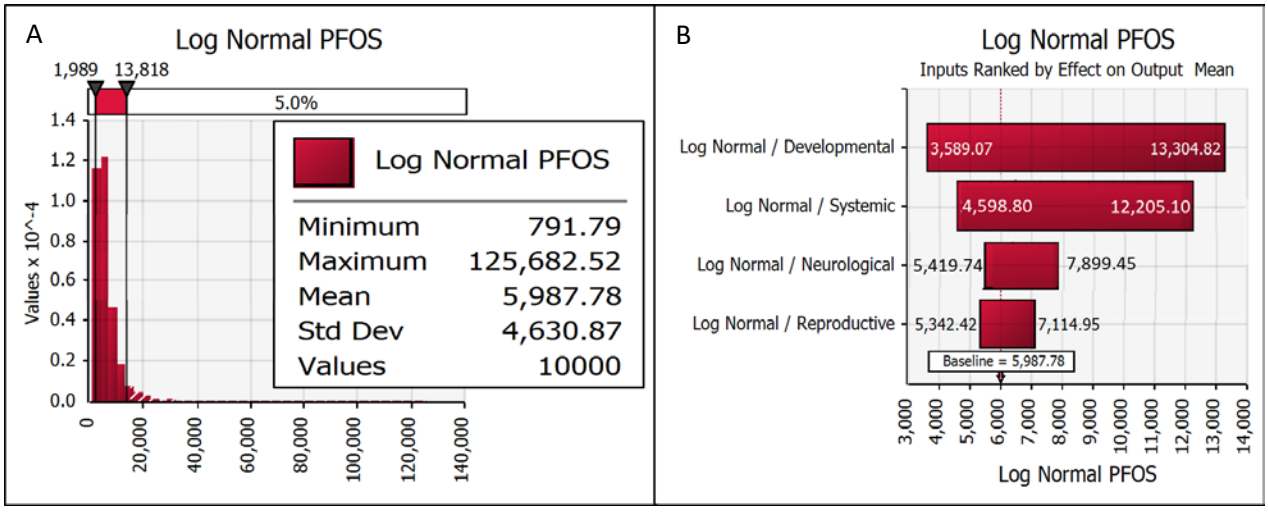


Figure 25: Monte Carlo Simulation Results for Intermediate Effect Factors of PFOS Using Varying Inputs of Symptom Distributions Assuming a Log-Normal Distribution Result. A shows the normal distribution results for the simulation. B shows the tornado plot with data ranges for varying symptoms with maximum and minimum values displayed.

Figure 26 shows the result from a Monte Carlo simulation combining the distributions of PFOA and PFOS to develop a single distribution that can be multiplied by the combined concentration of PFOA and PFOS to achieve the CTU value.

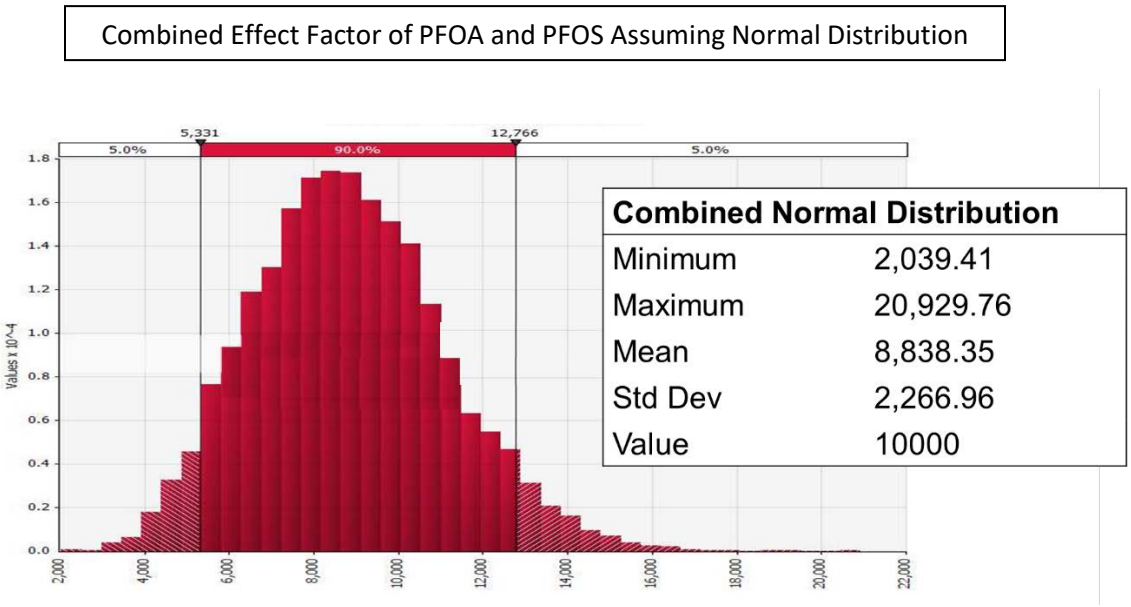


Figure 26: Monte Carlo Simulation Results for Intermediate Effect Factors for A Combined Concentration of PFOA and PFOS Using Varying Inputs of Symptom Distributions Assuming a Normal Distribution Result.

Figure 27 and Figure 28 show a combined CTU matrix for varying concentration of PFOA and PFOS and comparing those values to treatment technology impacts at combined concentrations of 0.7, 7.0, and 70 µg/L. The impacts of PFAS far outweigh the impacts of treatment (Figure 27 and 28); however, the lowest concentration analyzed by Emery (2019) is at a combined PFAS concentration of 700 parts per trillion which is 10 time greater than the EPA lifetime health advisory limit. For example, at a

concentration 0.3 ppt for PFOS and 0.4 ppt for PFOA, the CTU value would equal 1.3E-06 which greater than the CTU for GAC of 9.3E-08. Therefore, at these concentrations, treatment is the best option for limiting adverse human health effect. For concentrations below the lifetime advisory limit, PFAS impacts will eventually fall below the impacts of treatment as seen in the preliminary analysis results. The treatment impact data available cannot be accurately extrapolated to the levels required to determine the point at which treatment becomes more impactful to human health over the exposure to the PFAS concentration. Further research into treatment impacts at lower concentration of combined PFAS contamination will garner more applicable results from these concentrations matrices.

		Concentration of PFOS							
	μg/L	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7
Concentration of PFOA	0	0.0E+00	2.2E-07	4.4E-07	6.6E-07	8.9E-07	1.1E-06	1.3E-06	1.6E-06
	0.1	1.6E-07	3.8E-07	6.0E-07	8.2E-07	1.0E-06	1.3E-06	1.5E-06	
	0.2	3.1E-07	5.4E-07	7.6E-07	9.8E-07	1.2E-06	1.4E-06		
	0.3	4.7E-07	6.9E-07	9.2E-07	1.1E-06	1.4E-06			
	0.4	6.3E-07	8.5E-07	1.1E-06	1.3E-06				
	0.5	7.9E-07	1.0E-06	1.2E-06					
	0.6	9.4E-07	1.2E-06						
	0.7	1.1E-06							

		Concentration of PFOS							
	μg/L	0	1	2	3	4	5	6	7
Concentration of PFOA	0	0.0E+00	2.2E-06	4.4E-06	6.6E-06	8.9E-06	1.1E-05	1.3E-05	1.6E-05
	1	1.6E-06	3.8E-06	6.0E-06	8.2E-06	1.0E-05	1.3E-05	1.5E-05	
	2	3.1E-06	5.4E-06	7.6E-06	9.8E-06	1.2E-05	1.4E-05		
	3	4.7E-06	6.9E-06	9.2E-06	1.1E-05	1.4E-05			
	4	6.3E-06	8.5E-06	1.1E-05	1.3E-05				
	5	7.9E-06	1.0E-05	1.2E-05					
	6	9.4E-06	1.2E-05						
	7	1.1E-05							

		Concentration of PFOS							
	μg/L	0	10	20	30	40	50	60	70
Concentration of PFOA	0	0.0E+00	2.2E-05	4.4E-05	6.6E-05	8.9E-05	1.1E-04	1.3E-04	1.6E-04
	10	1.6E-05	3.8E-05	6.0E-05	8.2E-05	1.0E-04	1.3E-04	1.5E-04	
	20	3.1E-05	5.4E-05	7.6E-05	9.8E-05	1.2E-04	1.4E-04		
	30	4.7E-05	6.9E-05	9.2E-05	1.1E-04	1.4E-04			
	40	6.3E-05	8.5E-05	1.1E-04	1.3E-04				
	50	7.9E-05	1.0E-04	1.2E-04					
	60	9.4E-05	1.2E-04						
	70	1.1E-04							

Figure 27: PFOA and PFOS Concentration Matrix Assuming Different Distribution of CTUs Assuming Normal Distribution Results from Monte Carlo Simulations Compared to the Respective CTU Values for Treatment Impacts at 0.7, 7.0, and 70 µg/L with Red Denoting a Higher Impact Value for PFAS CTU

		Concentration of PFOS							
	μg/L	0	0.1	0.2	0.3	0.4	0.5	0.6	0.7
Concentration of PFOA	0	0.0E+00	1.4E-07	2.9E-07	4.3E-07	5.7E-07	7.1E-07	8.6E-07	1.0E-06
	0.1	8.4E-08	2.3E-07	3.7E-07	5.1E-07	6.5E-07	8.0E-07	9.4E-07	
	0.2	1.7E-07	3.1E-07	4.5E-07	6.0E-07	7.4E-07	8.8E-07		
	0.3	2.5E-07	4.0E-07	5.4E-07	6.8E-07	8.2E-07			
	0.4	3.4E-07	4.8E-07	6.2E-07	7.7E-07				
	0.5	4.2E-07	5.6E-07	7.1E-07					
	0.6	5.1E-07	6.5E-07						
	0.7	5.9E-07							

		Concentration of PFOS							
	μg/L	0	1	2	3	4	5	6	7
Concentration of PFOA	0	0.0E+00	1.4E-06	2.9E-06	4.3E-06	5.7E-06	7.1E-06	8.6E-06	1.0E-05
	1	8.4E-07	2.3E-06	3.7E-06	5.1E-06	6.5E-06	8.0E-06	9.4E-06	
	2	1.7E-06	3.1E-06	4.5E-06	6.0E-06	7.4E-06	8.8E-06		
	3	2.5E-06	4.0E-06	5.4E-06	6.8E-06	8.2E-06			
	4	3.4E-06	4.8E-06	6.2E-06	7.7E-06				
	5	4.2E-06	5.6E-06	7.1E-06					
	6	5.1E-06	6.5E-06						
	7	5.9E-06							

		Concentration of PFOS							
	μg/L	0	10	20	30	40	50	60	70
Concentration of PFOA	0	0.0E+00	1.4E-05	2.9E-05	4.3E-05	5.7E-05	7.1E-05	8.6E-05	1.0E-04
	10	8.4E-06	2.3E-05	3.7E-05	5.1E-05	6.5E-05	8.0E-05	9.4E-05	
	20	1.7E-05	3.1E-05	4.5E-05	6.0E-05	7.4E-05	8.8E-05		
	30	2.5E-05	4.0E-05	5.4E-05	6.8E-05	8.2E-05			
	40	3.4E-05	4.8E-05	6.2E-05	7.7E-05				
	50	4.2E-05	5.6E-05	7.1E-05					
	60	5.1E-05	6.5E-05						
	70	5.9E-05							

Figure 28: PFOA and PFOS Concentration Matrix Assuming Different Distribution of CTUs Assuming Log-Normal Distribution Results from Monte Carlo Simulations Compared to the Respective CTU Values for Treatment Impacts at 0.7, 7.0, and 70 µg/L with Red Denoting a Higher Impact Value for PFAS CTU

V. Conclusions and Recommendations

Overview

This thesis explored the toxicological impact of short and long chain PFAS at varying concentrations to determine at what PFAS concentrations levels do treatment technologies result in greater adverse health effects than the PFAS contamination alone. This study used a modified USEtox® toxicological model to develop comparable toxic unit graphs for varying concentrations. This data was used to determine the effect that animal species, adverse health symptoms, and gender had on the overall toxicological impact of PFAS and was then compared to prior investigations into adverse health effects of PFAS treatment technologies.

Conclusions

Does the species of animal used in animal testing have a significant effect when converted to human toxicology?

This study found that there were statistical differences in the effect factors derived from varying animal species. Mice were found to be statistically different from rats and monkeys in the data gathered for PFOA even after an animal-to-human conversion factor was applied. This contradicts expectations since the conversion factor was supposed to normalize the animal testing results for humans. This result could be a source of compounded error throughout the model for this study.

What is the difference between various adverse health symptoms as they relate to the risk assessment model of PFOA and PFOS?

The data collected from various animal tests shows that there was no statistical difference between the impacts of adverse health symptoms analyzed in this study (systemic, immune/lymphoret, neurological,

reproductive, and developmental). This indicates that no symptom is more prevalent than the others and therefore, exposure to PFAS is likely to manifest in all symptoms as concentrations increase.

What is the difference between genders in toxicological risk assessment of PFOA and PFOS?

Analysis of the effect of gender shows no statistical difference between the toxicological impact between males and females. Neither gender is statistically more likely to show signs of adverse health effects based on the data from this study.

What are the differences in toxicological risk assessment between short and long chain PFAS?

The results from the toxicological model (see Table 9) show that the impact of short chain PFAS falls far below comparable concentrations of PFOA and PFOS making their use a viable option based on toxicological impact assessments. With short chains resulting in far less toxicological impacts, this study concludes that short chains are a viable alternative to PFOA and PFOS from a toxicological risk assessment viewpoint; however, this study shows that there are still adverse impacts of short chain PFAS, just much less severe than their long chain counterparts. This means that short chain PFAS may not be the ideal alternatives since they still will result in adverse toxicological impacts. This study can also conclude that for concentrations of short chain PFAS remain less impactful than treatment technologies at concentrations less than 700 parts per trillion.

How do the risks of PFAS contamination compare to life cycle adverse health impact of treatment technologies?

Assuming the treatment data used in this research could be extrapolated, knowing that GAC and IEX would pull other contaminants and particles from water processed in a potable treatment plant, values at which treatment impacts exceed PFAS exposure can be determined. Under these conditions, treating PFOA and PFOS would benefit human health at concentrations of 11 and 17 parts per trillion

respectively while short chain PFAS and PFAS alternatives will stay less impactful until concentrations of 700 parts per trillion or higher.

Research Significance

This research shows that toxicological impact assessment can be determined based on contaminants found in groundwater utilizing the known concentrations of these chemicals. These impact assessments can be compared to the impacts of treatment technologies calibrated to the specific area in which the contaminants are found to determine those locations' treatment levels. The concentration at which treatment impacts fall below the impact of exposure should be the treatment level for which the contaminant is remediated.

The data used for this research was taken from published sources which impacts the significance of this research. First, relying on published sources for data limited the amount of data with some short chains only having a single data point. Furthermore, only using published data causes the results of this research to be negatively impacted by publication bias. Since significant results are more likely to be published, that data gathered is lacking the non-significant results of animal tests which introduces bias into this research and could skew the result in favor of the publication bias.

Recommendations for Future Research

This research focused on developing impact assessment of short and long chain PFAS compounds. These impacts, in Comparative Toxic Units, can be compared to impact assessment of treatment technologies to determine geographically based treatment levels for PFAS contamination. This data used in this research for treatment impacts is specific to Wright Patterson Air Force Base for which data was only available for PFAS concentrations of 0.7, 7.0, and 70 µg/L or 700, 7,000, and 70,000 parts per trillion. Utilizing the methodology of Emery et al, future research could develop a treatment curve for

varying PFAS contamination that could be compared to the results of this research to find more accurate treatment levels. This research can also be applied to varying locations as this model is not geographically based but based on groundwater contamination levels and should be a universally applied model regardless of location.

Future research into PFAS fate and transport and into PFAS exposure can refine this model resulting in more accurate CTU values allowing for better determination of treatment levels.

Appendix A: Data

PFOA Data								
References				LOAEL	NOAEL	ED50	AF_i	EF
Acute Exposure								
Death	Griffith and Long 1980	Monkey	M	100	25	225	1.9	11.80
	Griffith and Long 1980	Rat	M	680	170	1530	4.1	3.75
	Griffith and Long 1980	Rat	F	430	107.5	967.5	4.1	5.92
	Griffith and Long 1980	Rat	M	1000	250	2250	4.1	2.55
	Griffith and Long 1980	Rat	F	1130	282.5	2542.5	4.1	2.25
	Griffith and Long 1980	Mouse	M	180	45	405	7.3	25.20
	Griffith and Long 1980	Mouse	F	195	48.75	438.75	7.3	23.26
Systemic	Cook et al. 1992	Rat	M	1	0.25	2.25	4.1	2547.14
	Cook et al. 1992	Rat	M		10	90	4.1	63.68
	Cook et al. 1992	Rat	M	10	2.5	22.5	4.1	254.71
	Cook et al. 1992	Rat	M		25	225	4.1	25.47
	Elcombe et al. 2010	Rat	M	18	4.5	40.5	4.1	141.51
	Haughom and Spydevoid 1992	Rat	M	16	4	36	4.1	159.20
	Haughom and Spydevoid 1992	Rat	M		16	144	4.1	39.80
	Ikeda et al. 1985	Rat	M	20	5	45	4.1	127.36
	Iwai and Yamashita 2006	Rat	M		5	45	4.1	127.36
	Iwai and Yamashita 2006	Rat	M	50	12.5	112.5	4.1	50.94
	Iwai and Yamashita 2006	Rat	M		50	450	4.1	12.74
	Kawashima et al. 1995	Rat	M	4.7	1.175	10.575	4.1	541.94
	Kawashima et al. 1995	Rat	M		2.4	21.6	4.1	265.33
	Kawashima et al. 1995	Rat	M		38	342	4.1	16.76
	Liu et al. 1996	Rat	M		0.2	1.8	4.1	3183.92
	Liu et al. 1996	Rat	M	2	0.5	4.5	4.1	1273.57
	Liu et al. 1996	Rat	M		2	18	4.1	318.39
	Liu et al. 1996	Rat	M	20	5	45	4.1	127.36
	Pastoor et al. 1987	Rat	M	50	12.5	112.5	4.1	50.94
	Pastoor et al. 1987	Rat	M	50	12.5	112.5	4.1	50.94
	staples et al. 1984	Rat	F	100	25	225	4.1	25.47
	Hu et al. 2010	Mouse	F		1	9	7.3	1133.79
	Johansson et al. 2009	Mouse	M		8.7	78.3	7.3	130.32
	Kennedy 1987	Mouse	M	5.3	1.325	11.925	7.3	855.69
	Permadi et al. 1992	Mouse	M	78	19.5	175.5	7.3	58.14
	Permadi et al. 1992	Mouse	M	78	19.5	175.5	7.3	58.14
	Permadi et al. 1993	Mouse	M	78	19.5	175.5	7.3	58.14

PFOA Data								
	References			LOAEL	NOAEL	ED50	AF_i	EF
	Permadi et al. 1993	Mouse	M	78	19.5	175.5	7.3	58.14
	White et al. 2009	Mouse	F	5	1.25	11.25	7.3	907.03
	White et al. 2009	Mouse	F		5	45	7.3	226.76
	Wolf et al. 2007	Mouse	F	5	1.25	11.25	7.3	907.03
	Wolf et al. 2007	Mouse	M		20	180	7.3	56.69
	Xie et al. 2003	Mouse	M	24	6	54	7.3	188.96
	Xie et al. 2003	Mouse	M	24	6	54	7.3	188.96
	Yahia et al. 2010	Mouse	F	1	0.25	2.25	7.3	4535.15
	Yahia et al. 2010	Mouse	F	1	0.25	2.25	7.3	4535.15
	Yang et al. 2000	Mouse	M	30	7.5	67.5	7.3	151.17
	Yang et al. 2000	Mouse	M	30	7.5	67.5	7.3	151.17
	Yang et al. 2001	Mouse	M	1	0.25	2.25	7.3	4535.15
	Yang et al. 2002	Mouse	M	33	8.25	74.25	7.3	137.43
	Yang et al. 2002	Mouse	M	33	8.25	74.25	7.3	137.43
	Iwai and Yamashita 2006	Rat	M		50	450	4.1	12.74
	DeWitt et al. 2009	Mouse	F		7.5	67.5	7.3	151.17
	DeWitt et al. 2009	Mouse	F	15	3.75	33.75	7.3	302.34
Immuno/Lymphoret	Yang et al. 2000	Mouse	M	30	7.5	67.5	7.3	151.17
	Yang et al. 2001	Mouse	M	11.5	2.875	25.875	7.3	394.36
	Yang et al. 2002	Mouse	M	24	6	54	7.3	188.96
	Yang et al. 2002	Mouse	M	33	8.25	74.25	7.3	137.43
Neurological	Johansson et al. 2009	Mouse	M	8.7	2.175	19.575	7.3	521.28
	Biegel et al. 1995	Rat	M	25	6.25	56.25	4.1	101.89
	Cook et al. 1992	Rat	M	10	2.5	22.5	4.1	254.71
	Cook et al. 1992	Rat	M		1	9	4.1	636.78
Reproductive	Liu et al. 1996	Rat	M		0.2	1.8	4.1	3183.92
	Liu et al. 1996	Rat	M	2	0.5	4.5	4.1	1273.57
	White et al. 2009	Mouse	F	5	1.25	11.25	7.3	907.03
	staples et al. 1984	Rat	M		100	900	4.1	6.37
	Hu et al. 2010	Mouse	F	0.5	0.125	1.125	7.3	9070.29
	Johansson et al. 2008	Mouse	M	0.58	0.145	1.305	7.3	7819.22
	White et al. 2007	Mouse	F	5	1.25	11.25	7.3	907.03
Developmental	White et al. 2009	Mouse	F	5	1.25	11.25	7.3	907.03
	White et al. 2009	Mouse	F	5	1.25	11.25	7.3	907.03
	Wolf et al. 2007	Mouse	M	5	1.25	11.25	7.3	907.03
	Yahia et al. 2010	Mouse	F		1	9	7.3	1133.79
	Yahia et al. 2010	Mouse	F	5	1.25	11.25	7.3	907.03

PFOA Data								
	References			LOAEL	NOAEL	ED50	AF_i	EF
	Yahia et al. 2010	Mouse	F	5	1.25	11.25	7.3	907.03
	Gortner et al. 1982	Rabbit	F		50	450	2.4	7.46
Intermediate Exposure								
	Griffith and Long 1980	Monkey	M	30	7.5	67.5	1.9	39.35
Death	Griffith and Long 1980	Mouse	M	54	13.5	121.5	7.3	83.98
	Griffith and Long 1980	Mouse	F	58	14.5	130.5	7.3	78.19
	Butenhoff et al. 2002	Monkey	M		20	180	1.9	14.75
	Butenhoff et al. 2002	Monkey	M		20	180	1.9	14.75
	Butenhoff et al. 2002	Monkey	M		20	180	1.9	14.75
	Butenhoff et al. 2002	Monkey	M		20	180	1.9	14.75
	Butenhoff et al. 2002	Monkey	M	3	0.75	6.75	1.9	393.46
	Butenhoff et al. 2002	Monkey	M		20	180	1.9	14.75
	Butenhoff et al. 2002	Monkey	M		3	27	1.9	98.37
	Butenhoff et al. 2002	Monkey	M	10	2.5	22.5	1.9	118.04
	Butenhoff et al. 2002	Monkey	M		20	180	1.9	14.75
	Butenhoff et al. 2002	Monkey	M		20	180	1.9	14.75
	Butenhoff et al. 2002	Monkey	M		10	90	1.9	29.51
	Butenhoff et al. 2002	Monkey	M	20	5	45	1.9	59.02
	Griffith and Long 1980	Monkey	M		10	90	1.9	29.51
	Griffith and Long 1980	Monkey	M		10	90	1.9	29.51
	Griffith and Long 1980	Monkey	M	30	7.5	67.5	1.9	39.35
Systemic	Griffith and Long 1980	Monkey	M		30	270	1.9	9.84
	Griffith and Long 1980	Monkey	M		10	90	1.9	29.51
	Griffith and Long 1980	Monkey	M		10	90	1.9	29.51
	Griffith and Long 1980	Monkey	M		10	90	1.9	29.51
	Griffith and Long 1980	Monkey	M	30	7.5	67.5	1.9	39.35
	Griffith and Long 1980	Monkey	M		10	90	1.9	29.51
	Griffith and Long 1980	Monkey	M	30	7.5	67.5	1.9	39.35
	Thomford 2010	Monkey	M		20	180	1.9	14.75
	Thomford 2010	Monkey	M		20	180	1.9	14.75
	Thomford 2010	Monkey	M		20	180	1.9	14.75
	Thomford 2010	Monkey	M		20	180	1.9	14.75
	Biegel et al. 2001	Rat	M	13.6	3.4	30.6	4.1	187.29
	Biegel et al. 2001	Rat	M	13.6	3.4	30.6	4.1	187.29
	Butenhoff et al. 2004	Rat	M	3	0.75	6.75	4.1	849.05
	Butenhoff et al. 2004	Rat	M	3	0.75	6.75	4.1	849.05
	Butenhoff et al. 2004	Rat	M	30	7.5	67.5	4.1	84.90

PFOA Data							
References			LOAEL	NOAEL	ED50	AF_i	EF
Butenhoff et al. 2004	Rat	M		10	90	4.1	63.68
Butenhoff et al. 2004	Rat	M	10	2.5	22.5	4.1	254.71
Butenhoff et al. 2004	Rat	M		3	27	4.1	212.26
Cui et al. 2009	Rat	M	5	1.25	11.25	4.1	509.43
Cui et al. 2009	Rat	M	5	1.25	11.25	4.1	509.43
Elcombe et al. 2010	Rat	M	18	4.5	40.5	4.1	141.51
Griffith and Long 1980	Rat	F		110	990	4.1	5.79
Griffith and Long 1980	Rat	F		110	990	4.1	5.79
Griffith and Long 1980	Rat	F		110	990	4.1	5.79
Griffith and Long 1980	Rat	F		110	990	4.1	5.79
Griffith and Long 1980	Rat	F		110	990	4.1	5.79
Griffith and Long 1980	Rat	M		1	9	4.1	636.78
Griffith and Long 1980	Rat	M	3	0.75	6.75	4.1	849.05
Griffith and Long 1980	Rat	F		110	990	4.1	5.79
Griffith and Long 1980	Rat	F		110	990	4.1	5.79
Griffith and Long 1980	Rat	F		110	990	4.1	5.79
Griffith and Long 1980	Rat	F		110	990	4.1	5.79
Griffith and Long 1980	Rat	M		30	270	4.1	21.23
Griffith and Long 1980	Rat	M	100	25	225	4.1	25.47
Griffith and Long 1980	Rat	F		110	990	4.1	5.79
Griffith and Long 1980	Rat	M	3	0.75	6.75	4.1	849.05
Griffith and Long 1980	Rat	M	30	7.5	67.5	4.1	84.90
Griffith and Long 1980	Rat	M		10	90	4.1	63.68
Griffith and Long 1980	Rat	M	100	25	225	4.1	25.47
Loveless et al. 2008	Rat	M		29	261	4.1	21.96
Loveless et al. 2008	Rat	M	0.28	0.07	0.63	4.1	9096.92
Loveless et al. 2008	Rat	M	0.96	0.24	2.16	4.1	2653.27
Loveless et al. 2008	Rat	M		96	864	4.1	6.63
Perkins et al. 2004	Rat	M		6.5	58.5	4.1	97.97
Perkins et al. 2004	Rat	M		0.64	5.76	4.1	994.98
Perkins et al. 2004	Rat	M	0.06	0.015	0.135	4.1	42452.29
Perkins et al. 2004	Rat	M		6.5	58.5	4.1	97.97
Abbott et al. 2007	Mouse	F		0.6	5.4	7.3	1889.64
Abbott et al. 2007	Mouse	F	1	0.25	2.25	7.3	4535.15
Abbott et al. 2007	Mouse	F		10	90	7.3	113.38
Albrecht et al. 2013	Mouse	F	3	0.75	6.75	7.3	1511.72
Dewitt et al. 2008	Mouse	F		7.5	67.5	7.3	151.17

PFOA Data								
References				LOAEL	NOAEL	ED50	AF_i	EF
	Dewitt et al. 2008	Mouse	F	15	3.75	33.75	7.3	302.34
	Griffith and Long 1980	Mouse	M	5.4	1.35	12.15	7.3	839.84
	Griffith and Long 1980	Mouse	M	5.4	1.35	12.15	7.3	839.84
	Griffith and Long 1980	Mouse	F	5.8	1.45	13.05	7.3	781.92
	Kennedy 1987	Mouse	M	0.5	0.125	1.125	7.3	9070.29
	Kennedy 1987	Mouse	M		0.2	1.8	7.3	5668.93
	Lau et al. 2006	Mouse	F	1	0.25	2.25	7.3	4535.15
	Lau et al. 2006	Mouse	F		5	45	7.3	226.76
	Lau et al. 2006	Mouse	F	10	2.5	22.5	7.3	453.51
	Loveless et al. 2008	Mouse	M		0.96	8.64	7.3	1181.03
	Loveless et al. 2008	Mouse	M	0.29	0.0725	0.6525	7.3	15638.44
	Loveless et al. 2008	Mouse	M	9.6	2.4	21.6	7.3	472.41
	Son et al. 2008	Mouse	M	0.5	0.125	1.125	7.3	9070.29
	Son et al. 2008	Mouse	M		47	423	7.3	24.12
	Son et al. 2008	Mouse	M		2.6	23.4	7.3	436.07
	Son et al. 2008	Mouse	M	18	4.5	40.5	7.3	251.95
	Tan et al. 2013	Mouse	M	5	1.25	11.25	7.3	907.03
	Wolf et al. 2007	Mouse	F	3	0.75	6.75	7.3	1511.72
	Wolf et al. 2007	Mouse	F		5	45	7.3	226.76
	Butenhoff et al. 2002	Monkey	M		20	180	1.9	14.75
	Griffith and Long 1980	Monkey	M		10	90	1.9	29.51
	Griffith and Long 1980	Monkey	M	30	7.5	67.5	1.9	39.35
	Griffith and Long 1980	Rat	F		110	990	4.1	5.79
	Loveless et al. 2008	Rat	M		29	261	4.1	21.96
Immuno/ Lymphoret	Dewitt et al. 2008	Mouse	F		1.88	16.92	7.3	603.08
	Dewitt et al. 2008	Mouse	F	3.75	0.9375	8.4375	7.3	1209.37
	Loveless et al. 2008	Mouse	M	9.6	2.4	21.6	7.3	472.41
	Loveless et al. 2008	Mouse	M		0.96	8.64	7.3	1181.03
	Son et al. 2008	Mouse	M	47.21	11.8025	106.2225	7.3	96.06
	Son et al. 2008	Mouse	M	0.49	0.1225	1.1025	7.3	9255.40
	Butenhoff et al. 2002	Monkey	M		20	180	1.9	14.75
	Griffith and Long 1980	Monkey	M		10	90	1.9	29.51
	Griffith and Long 1980	Monkey	M	30	7.5	67.5	1.9	39.35
Neruological	Cui et al. 2009	Rat	M	5	1.25	11.25	4.1	509.43
	Griffith and Long 1980	Rat	F		110	990	4.1	5.79
	Perkins et al. 2004	Rat	M		6.5	58.5	4.1	97.97
Reporductive	Butenhoff et al. 2002	Monkey	M		20	180	1.9	14.75

PFOA Data								
	References			LOAEL	NOAEL	ED50	AF_i	EF
	Griffith and Long 1980	Monkey	M		100	900	1.9	2.95
	Thomford 2001	Monkey	M		20	180	1.9	14.75
	Biegel et al. 2001	Rat	M	13.6	3.4	30.6	4.1	187.29
	Butenhoff et al. 2004	Rat	M		30	270	4.1	21.23
	Griffith and Long 1980	Rat	M		100	900	4.1	6.37
	Griffith and Long 1980	Rat	F		110	990	4.1	5.79
	Perkins et al. 2004	Rat	M		6.5	58.5	4.1	97.97
	White et al. 2007	Mouse	F	5	1.25	11.25	7.3	907.03
	White et al. 2011	Mouse	F	1	0.25	2.25	7.3	4535.15
	White et al. 2011	Mouse	F	0.001	0.00025	0.00225	7.3	4535147.39
	Butenhoff et al. 2004	Rat	M	3	0.75	6.75	4.1	849.05
	Butenhoff et al. 2004	Rat	M	30	7.5	67.5	4.1	84.90
	Cheng et al. 2013	Rat	M	1.6	0.4	3.6	4.1	1591.96
	Abbott et al. 2007	Mouse	M		0.3	2.7	7.3	3779.29
	Abbott et al. 2007	Mouse	M	0.6	0.15	1.35	7.3	7558.58
	Albrecht et al. 2013	Mouse	M	3	0.75	6.75	7.3	1511.72
	Hines et al. 2009	Mouse	F	5	1.25	11.25	7.3	907.03
	Hines et al. 2009	Mouse	F	0.01	0.0025	0.0225	7.3	453514.74
	Lau et al. 2006	Mouse	M	3	0.75	6.75	7.3	1511.72
	Lau et al. 2006	Mouse	M	5	1.25	11.25	7.3	907.03
Developmental	Macon et al. 2011	Mouse	F	0.3	0.075	0.675	7.3	15117.16
	Macon et al. 2011	Mouse	F	0.01	0.0025	0.0225	7.3	453514.74
	Onishchenko et al. 2011	Mouse	M	0.3	0.075	0.675	7.3	15117.16
	White et al. 2007	Mouse	M	5	1.25	11.25	7.3	907.03
	White et al. 2009	Mouse	F	3	0.75	6.75	7.3	1511.72
	White et al. 2011	Mouse	F	5	1.25	11.25	7.3	907.03
	White et al. 2011	Mouse	F		1	9	7.3	1133.79
	White et al. 2011	Mouse	F	0.001	0.00025	0.00225	7.3	4535147.39
	Wolf et al. 2007	Mouse	M	5	1.25	11.25	7.3	907.03
	Wolf et al. 2007	Mouse	M	3	0.75	6.75	7.3	1511.72
		Chronic						
	3M 1983	Rat	M	15	3.75	33.75	4.1	169.81
	3M 1983	Rat	M		1.5	13.5	4.1	424.52
Systemic	3M 1983	Rat	M		15	135	4.1	42.45
	3M 1983	Rat	M		15	135	4.1	42.45
	3M 1983	Rat	M		15	135	4.1	42.45
	3M 1983	Rat	M	1.5	0.375	3.375	4.1	1698.09

PFOA Data								
References				LOAEL	NOAEL	ED50	AF_i	EF
	3M 1983	Rat	M	15	3.75	33.75	4.1	169.81
	3M 1983	Rat	M		15	135	4.1	42.45
	3M 1983	Rat	M		15	135	4.1	42.45
	3M 1983	Rat	F		1.5	13.5	4.1	424.52
	3M 1983	Rat	F	15	3.75	33.75	4.1	169.81
	3M 1983	Rat	M	1.5	0.375	3.375	4.1	1698.09
	Biegel et al. 2001	Rat	M	13.6	3.4	30.6	4.1	187.29
	Biegel et al. 2001	Rat	M	13.6	3.4	30.6	4.1	187.29
	Biegel et al. 2001	Rat	M	13.6	3.4	30.6	4.1	187.29
Immuno/Lymphoret	3M 1983	Rat	M		15	135	4.1	42.45
Neruological	3M 1983	Rat	M		15	135	4.1	42.45
Reproductive	3M 1983	Rat	M		1.5	13.5	4.1	424.52
	3M 1983	Rat	M	15	3.75	33.75	4.1	169.81
	3M 1983	Rat	F	1.5	0.375	3.375	4.1	1698.09
	Biegel et al. 2001	Rat	M	13.6	3.4	30.6	4.1	187.29

PFOS Data								
	Reference			LOAEL	NOAEL	ED50	AFi	EF
Acute Exposure								
Systemic	Chang et al. 2008	Rat	M	15	3.75	33.75	4.1	169.81
	Elcombe et al. 2012a	Rat	M		10.30	92.7	4.1	61.82
	Elcombe et al. 2012a	Rat	M		10.30	92.7	4.1	61.82
	Elcombe et al. 2012a	Rat	M	8.17	2.04	18.3825	4.1	311.77
	Elcombe et al. 2012a	Rat	M		1.72	15.48	4.1	370.22
	Elcombe et al. 2012a	Rat	M		8.17	73.53	4.1	77.94
	Elcombe et al. 2012b	Rat	M	1.79	0.45	4.0275	4.1	1422.98
	Elcombe et al. 2012b	Rat	M		8.96	80.64	4.1	71.07
	Grasty et al. 2003	Rat	F	25	6.25	56.25	4.1	101.89
	Haughom and Spydevol 1992	Rat	M	15	3.75	33.75	4.1	169.81
	Haughom and Spydevol 1992	Rat	M		15.00	135	4.1	42.45
	Era et al. 2006	Mouse	F	20	5.00	45	7.3	226.76
	Fuentes et al. 2006	Mouse	F		1.50	13.5	7.3	755.86
	Fuentes et al. 2006	Mouse	F	3	0.75	6.75	7.3	1511.72
	Fuentes et al. 2006	Mouse	F		6.00	54	7.3	188.96
	Fuentes et al. 2006	Mouse	F		6.00	54	7.3	188.96
	Fuentes et al. 2007	Mouse	F		6.00	54	7.3	188.96
	Johansson et al. 2009	Mouse	M		11.30	101.7	7.3	100.34
	Wan et al. 2011	Mouse	M		1.00	9	7.3	1133.79
	Wan et al. 2011	Mouse	M	5	1.25	11.25	7.3	907.03
	Wan et al. 2011	Mouse	M		10.00	90	7.3	113.38
	Case et al. 2001	Rabbit	F		0.10	0.9	2.4	3727.52
	Case et al. 2001	Rabbit	F	1	0.25	2.25	2.4	1491.01
Immuno/Lymphoret	Zheng et al. 2009	Mouse	M	5	1.25	11.25	7.3	907.03
Neurological	Johansson et al. 2009	Mouse	M	11.3	2.83	25.425	7.3	401.34
Reproductive	Wan et al. 2011	Mouse	M		10.00	90	7.3	113.38
	Case et al. 2001	Rabbit	M	3.75	0.94	8.4375	2.4	397.60
	Case et al. 2001	Rabbit	M		2.50	22.5	2.4	149.10
Developmental	Grasty et al. 2003	Rat	M	25	6.25	56.25	4.1	101.89
	Grasty et al. 2003	Rat	M	25	6.25	56.25	4.1	101.89
	Grasty et al. 2003	Rat	M	25	6.25	56.25	4.1	101.89
	Abbott et al. 2009	Mouse	M	4.5	1.13	10.125	7.3	1007.81
	Era et al. 2009	Mouse	F	50	12.50	112.5	7.3	90.70
	Fuentes et al. 2006	Mouse	M		6.00	54	7.3	188.96
	Fuentes et al. 2007	Mouse	M	6	1.50	13.5	7.3	755.86
	Johansson et al. 2009	Mouse	M	0.75	0.19	1.6875	7.3	6046.86

PFOS Data								
	Reference			LOAEL	NOAEL	ED50	AFi	EF
	Case et al. 2001	Rabbit	F		1.00	9	2.4	372.75
	Case et al. 2001	Rabbit	F	2.5	0.63	5.625	2.4	596.40
	Case et al. 2001	Rabbit	F	3.75	0.94	8.4375	2.4	397.60
Intermediate								
Death	Cui et al. 2001	Rat	M	20	5	45	4.1	127.36
	Seacat et al. 2002	Monkey	M		0.75	6.75	1.9	393.46
	Seacat et al. 2002	Monkey	M		0.75	6.75	1.9	393.46
	Seacat et al. 2002	Monkey	M		0.75	6.75	1.9	393.46
	Seacat et al. 2002	Monkey	M		0.75	6.75	1.9	393.46
	Seacat et al. 2002	Monkey	M		0.75	6.75	1.9	393.46
	Seacat et al. 2002	Monkey	M		0.15	1.35	1.9	1967.30
	Seacat et al. 2002	Monkey	M	0.75	0.19	1.6875	1.9	1573.84
	Seacat et al. 2002	Monkey	M		0.75	6.75	1.9	393.46
	Seacat et al. 2002	Monkey	M	0.75	0.19	1.6875	1.9	1573.84
	Seacat et al. 2002	Monkey	M		0.15	1.35	1.9	1967.30
	Seacat et al. 2002	Monkey	M	0.75	0.19	1.6875	1.9	1573.84
	Seacat et al. 2002	Monkey	M	0.75	0.19	1.6875	1.9	1573.84
	Seacat et al. 2002	Monkey	M	0.15	0.04	0.3375	1.9	7869.21
	Seacat et al. 2002	Monkey	M		0.75	6.75	1.9	393.46
	Seacat et al. 2002	Monkey	M	0.75	0.19	1.6875	1.9	1573.84
Systemic	Thomford 2002	Monkey	M		2.00	18	1.9	147.55
	Thomford 2002	Monkey	M		2.00	18	1.9	147.55
	Thomford 2002	Monkey	M		2.00	18	1.9	147.55
	Thomford 2002	Monkey	M		2.00	18	1.9	147.55
	Thomford 2002	Monkey	M		2.00	18	1.9	147.55
	Thomford 2002	Monkey	M		2.00	18	1.9	147.55
	Thomford 2002	Monkey	M		2.00	18	1.9	147.55
	Cui et al. 2009	Rat	M	5	1.25	11.25	4.1	509.43
	Cui et al. 2009	Rat	M	5	1.25	11.25	4.1	509.43
	Curran et al. 2008	Rat	M		5.89	53.01	4.1	108.11
	Curran et al. 2008	Rat	M		3.47	31.23	4.1	183.51
	Curran et al. 2008	Rat	M	7.01	1.75	15.7725	4.1	363.36
	Curran et al. 2008	Rat	M	0.14	0.04	0.315	4.1	18193.84
	Curran et al. 2008	Rat	M		5.89	53.01	4.1	108.11
	Curran et al. 2008	Rat	M		0.14	1.26	4.1	4548.46
	Curran et al. 2008	Rat	M	1.23	0.31	2.7675	4.1	2070.84
	Elcombe et al. 2012	Rat	M	1.54	0.39	3.465	4.1	1653.99

PFOS Data							
Reference			LOAEL	NOAEL	ED50	AFi	EF
Elcombe et al. 2012	Rat	M		7.34	66.06	4.1	86.76
Lefebvre et al. 2008	Rat	M	0.14	0.04	0.315	4.1	18193.84
Lefebvre et al. 2008	Rat	M		1.33	11.97	4.1	478.79
Lefebvre et al. 2008	Rat	M	3.21	0.80	7.2225	4.1	793.50
Luebker et al. 2005a	Rat	M		1.60	14.4	4.1	397.99
Luebker et al. 2005a	Rat	M	3.2	0.80	7.2	4.1	795.98
Luebker et al. 2005b	Rat	F	0.4	0.10	0.9	4.1	6367.84
Luebker et al. 2005b	Rat	F	0.4	0.10	0.9	4.1	6367.84
Luebker et al. 2005b	Rat	F		1.60	14.4	4.1	397.99
Luebker et al. 2005b	Rat	F	2	0.50	4.5	4.1	1273.57
Seacat et al. 2003	Rat	F		1.77	15.93	4.1	359.77
Seacat et al. 2003	Rat	F		1.77	15.93	4.1	359.77
Seacat et al. 2003	Rat	F		1.77	15.93	4.1	359.77
Seacat et al. 2003	Rat	F		1.77	15.93	4.1	359.77
Seacat et al. 2003	Rat	F		1.77	15.93	4.1	359.77
Seacat et al. 2003	Rat	F		1.77	15.93	4.1	359.77
Seacat et al. 2003	Rat	M	1.33	0.33	2.9925	4.1	1915.14
Seacat et al. 2003	Rat	M		0.34	3.06	4.1	1872.90
Seacat et al. 2003	Rat	M		0.34	3.06	4.1	1872.90
Seacat et al. 2003	Rat	M	1.33	0.33	2.9925	4.1	1915.14
Seacat et al. 2003	Rat	F		1.56	14.04	4.1	408.20
Seacat et al. 2003	Rat	F		1.56	14.04	4.1	408.20
Seacat et al. 2003	Rat	F		1.56	14.04	4.1	408.20
Seacat et al. 2003	Rat	F		1.56	14.04	4.1	408.20
Thibodeaux et al. 2003	Rat	F	5	1.25	11.25	4.1	509.43
Thibodeaux et al. 2003	Rat	F		1.00	9	4.1	636.78
Thibodeaux et al. 2003	Rat	F	1	0.25	2.25	4.1	2547.14
Thibodeaux et al. 2003	Rat	F	2	0.50	4.5	4.1	1273.57
Thibodeaux et al. 2003	Rat	F		1.00	9	4.1	636.78
Thibodeaux et al. 2003	Rat	F	5	1.25	11.25	4.1	509.43
Yu et al. 2009a	Rat	M	0.27	0.07	0.6075	4.1	9433.84
Era et al. 2009	Mouse	F	20	5.00	45	7.3	226.76
Keil et al. 2008	Mouse	F		5.00	45	7.3	226.76
Thibodeaux et al. 2003	Mouse	F	5	1.25	11.25	7.3	907.03
Thibodeaux et al. 2003	Mouse	F		1.00	9	7.3	1133.79
Thibodeaux et al. 2003	Mouse	F		15.00	135	7.3	75.59
Thibodeaux et al. 2003	Mouse	F	20	5.00	45	7.3	226.76

PFOS Data								
	Reference			LOAEL	NOAEL	ED50	AFi	EF
	Thibodeaux et al. 2003	Mouse	F		20.00	180	7.3	56.69
	Wan et al. 2011	Mouse	M		1.00	9	7.3	1133.79
	Wan et al. 2011	Mouse	M	5	1.25	11.25	7.3	907.03
	Wan et al. 2011	Mouse	M	10	2.50	22.5	7.3	453.51
	Wan et al. 2011	Mouse	M		5.00	45	7.3	226.76
	Yahia et al. 2008	Mouse	F	10	2.50	22.5	7.3	453.51
	Yahia et al. 2008	Mouse	F		1.00	9	7.3	1133.79
	Seacat et al. 2002	Monkey	M		0.75	6.75	1.9	393.46
	Thomford 2002	Monkey	M		2.00	18	1.9	147.55
	Lefebvre et al. 2008	Rat	M		6.34	57.06	4.1	100.44
	Seacat et al. 2003	Rat	M		1.77	15.93	4.1	359.77
	Seacat et al. 2003	Rat	M		1.56	14.04	4.1	408.20
	Dong et al. 2009	Mouse	M		0.01	0.0747	7.3	136600.83
	Dong et al. 2009	Mouse	M	0.083	0.02	0.18675	7.3	54640.33
	Dong et al. 2011	Mouse	M	0.0833	0.02	0.187425	7.3	54443.55
	Dong et al. 2011	Mouse	M		0.02	0.1503	7.3	67891.43
	Guruge et al. 2009	Mouse	M		0.01	0.045	7.3	226757.37
	Guruge et al. 2009	Mouse	M	0.025	0.01	0.05625	7.3	181405.90
	Peden-Adams et al. 2008	Mouse	M	0.00166	0.00	0.003735	7.3	2732016.50
	Peden-Adams et al. 2008	Mouse	M		0.00	0.001494	7.3	6830041.25
	Seacat et al. 2002	Monkey	M		0.75	6.75	1.9	393.46
	Cui et al. 2009	Rat	M	5	1.25	11.25	4.1	509.43
	Kawamoto et al. 2011	Rat	M	8.5	2.13	19.125	4.1	299.66
	Kawamoto et al. 2011	Rat	M		2.00	18	4.1	318.39
Neurological	Seacat et al. 2003	Rat	M		1.77	15.93	4.1	359.77
	Seacat et al. 2003	Rat	F		1.56	14.04	4.1	408.20
	Long et al. 2013	Mouse	M		0.43	3.87	7.3	2636.71
	Long et al. 2013	Mouse	M	2.15	0.54	4.8375	7.3	2109.37
	Seacat et al. 2002	Monkey	M	0.75	0.19	1.6875	1.9	1573.84
	Seacat et al. 2002	Monkey	M		0.15	1.35	1.9	1967.30
	Thomford 2002	Monkey	M		2.00	18	1.9	147.55
	Butenhoff et al. 2009	Rat	F		1.00	9	4.1	636.78
Reproductive	Luebker et al. 2005a	Rat	M		3.20	28.8	4.1	199.00
	Luebker et al. 2005b	Rat	F		2.00	18	4.1	318.39
	Seacat et al. 2003	Rat	M		1.51	13.59	4.1	421.71
	Seacat et al. 2003	Rat	F		1.77	15.93	4.1	359.77
	Seacat et al. 2003	Rat	M		1.33	11.97	4.1	478.79

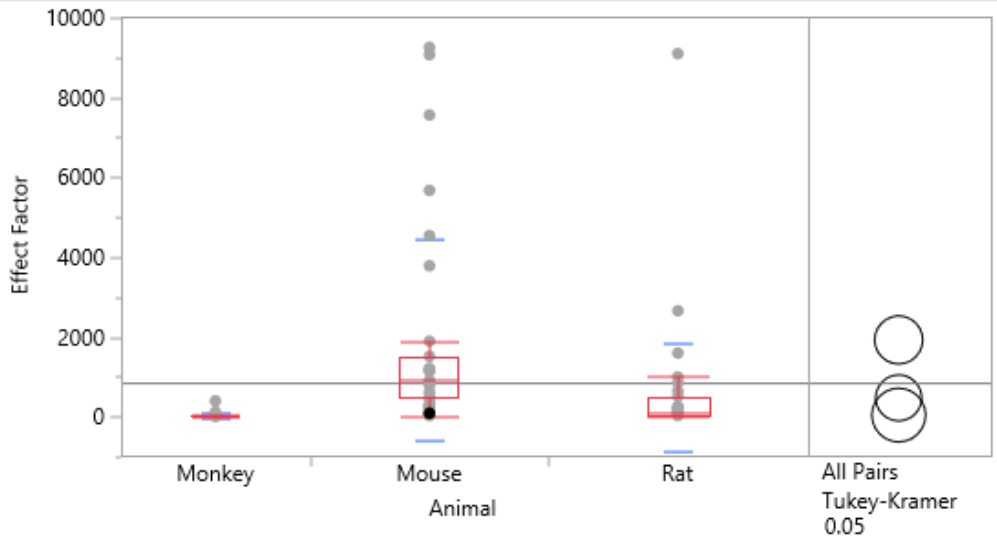
PFOS Data								
	Reference			LOAEL	NOAEL	ED50	AFi	EF
	Seacat et al. 2003	Rat	F		1.56	14.04	4.1	408.20
	Wan et al. 2011	Mouse	M		5.00	45	7.3	226.76
	Wan et al. 2011	Mouse	M	10	2.50	22.5	7.3	453.51
	Butenhoff et al. 2009	Rat	M	1	0.25	2.25	4.1	2547.14
	Butenhoff et al. 2009	Rat	M		0.30	2.7	4.1	2122.61
	Chang et al. 2009	Rat	F	1	0.25	2.25	4.1	2547.14
	Chen et al. 2012	Rat	M		0.10	0.9	4.1	6367.84
	Chen et al. 2012	Rat	M	2	0.50	4.5	4.1	1273.57
	Lau et al. 2003	Rat	M	2	0.50	4.5	4.1	1273.57
	Lau et al. 2003	Rat	M	1	0.25	2.25	4.1	2547.14
	Luebker et al. 2005	Rat	F	1.6	0.40	3.6	4.1	1591.96
	Luebker et al. 2005	Rat	M	1.6	0.40	3.6	4.1	1591.96
	Luebker et al. 2005	Rat	M	0.4	0.10	0.9	4.1	6367.84
	Luebker et al. 2005	Rat	M	0.4	0.10	0.9	4.1	6367.84
	Luebker et al. 2005	Rat	M	1.6	0.40	3.6	4.1	1591.96
	Thibodeaux et al. 2003	Rat	F	10	2.50	22.5	4.1	254.71
	Xia et al. 2011	Rat	M	2	0.50	4.5	4.1	1273.57
Developmental	Xia et al. 2011	Rat	M		0.60	5.4	4.1	1061.31
	Yu et al. 2009b	Rat	F	3.2	0.80	7.2	4.1	795.98
	Era et al. 2009	Mouse	F	20	5.00	45	7.3	226.76
	Keil et al. 2008	Mouse	M	1	0.25	2.25	7.3	4535.15
	Keil et al. 2008	Mouse	M		0.10	0.9	7.3	11337.87
	Lau et al. 2003	Mouse	M	1	0.25	2.25	7.3	4535.15
	Lau et al. 2003	Mouse	M	10	2.50	22.5	7.3	453.51
	Onishchenko et al. 2011	Mouse	M	0.3	0.08	0.675	7.3	15117.16
	Rosen et al. 2009	Mouse	M	5	1.25	11.25	7.3	907.03
	Thibodeaux et al. 2003	Mouse	F	5	1.25	11.25	7.3	907.03
	Thibodeaux et al. 2003	Mouse	F	20	5.00	45	7.3	226.76
	Thibodeaux et al. 2003	Mouse	F		1.00	9	7.3	1133.79
	Yahia et al. 2008	Mouse	F	20	5.00	45	7.3	226.76
	Yahia et al. 2008	Mouse	F	1	0.25	2.25	7.3	4535.15
	Yahia et al. 2008	Mouse	M	10	2.50	22.5	7.3	453.51
				Chronic				
	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29
Systemic	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29
	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29
	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29

PFOS Data								
	Reference			LOAEL	NOAEL	ED50	AFi	EF
	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29
	Butenhoff et al. 2012	Rat	M		0.5	4.5	4.1	1273.57
	Butenhoff et al. 2012	Rat	M	0.1	0.025	0.225	4.1	25471.38
	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29
	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29
	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29
	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29
	Butenhoff et al. 2012	Rat	F		0.25	2.25	4.1	2547.14
	Butenhoff et al. 2012	Rat	F	1.04	0.26	2.34	4.1	2449.17
Immuno/Lymphoret	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29
Neurological	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29
Reproductive	Butenhoff et al. 2012	Rat	M		1.04	9.36	4.1	612.29

Appendix B: Full Statistical Data

Fit Group

Oneway Analysis of Effect Factor By Animal



Oneway Anova

Summary of Fit

Rsquare	0.182666
Adj Rsquare	0.169794
Root Mean Square Error	1705.116
Mean of Response	852.295
Observations (or Sum Wgts)	130

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Animal	2	82521898	41260949	14.1916	<.0001*
Error	127	369242247	2907419.3		
C. Total	129	451764145			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Monkey	36	39.02	284.19	-523	601.4
Mouse	45	1921.70	254.18	1419	2424.7
Rat	49	467.70	243.59	-14	949.7

Std Error uses a pooled estimate of error variance

Means Comparisons

Comparisons for all pairs using Tukey-Kramer HSD

Confidence Quantile

q*	Alpha
2.37154	0.05

Fit Group

Oneway Analysis of Effect Factor By Animal

Means Comparisons

Comparisons for all pairs using Tukey-Kramer HSD

HSD Threshold Matrix

Abs(Dif)-HSD

	Mouse	Rat	Monkey
Mouse	-852.50	619.08	978.47
Rat	619.08	-816.96	-458.97
Monkey	978.47	-458.97	-953.12

Positive values show pairs of means that are significantly different.

Connecting Letters Report

Level		Mean
Mouse	A	1921.6981
Rat	B	467.6996
Monkey	B	39.0181

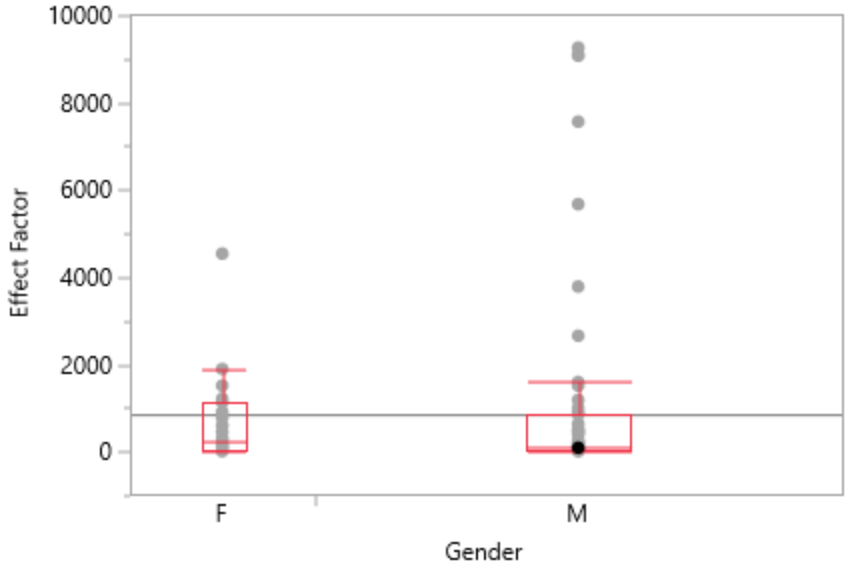
Levels not connected by same letter are significantly different.

Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Mouse	Monkey	1882.680	381.2754	978.470	2786.890	<.0001*
Mouse	Rat	1453.999	352.0574	619.080	2288.917	0.0002*
Rat	Monkey	428.681	374.2950	-458.974	1316.337	0.4881

Fit Group

Oneway Analysis of Effect Factor By Gender



Oneway Anova

Summary of Fit

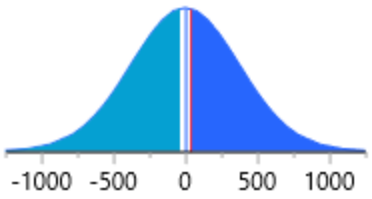
Rsquare	0.000067
Adj Rsquare	-0.00775
Root Mean Square Error	1878.609
Mean of Response	852.295
Observations (or Sum Wgts)	130

t Test

M-F

Assuming equal variances

Difference	34.70	t Ratio	0.092548
Std Err Dif	374.92	DF	128
Upper CL Dif	776.53	Prob > |t|	0.9264
Lower CL Dif	-707.14	Prob > t	0.4632
Confidence	0.95	Prob < t	0.5368



Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Gender	1	30228	30228	0.0086	0.9264
Error	128	451733918	3529171		
C. Total	129	451764145			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
F	34	826.672	322.18	189.19	1464.2
M	96	861.370	191.73	481.99	1240.7

Std Error uses a pooled estimate of error variance

t Test

M-F

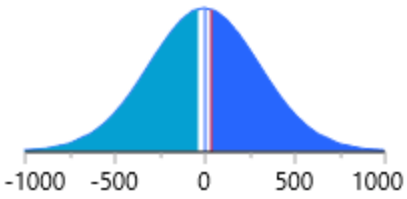
Fit Group

Oneway Analysis of Effect Factor By Gender

t Test

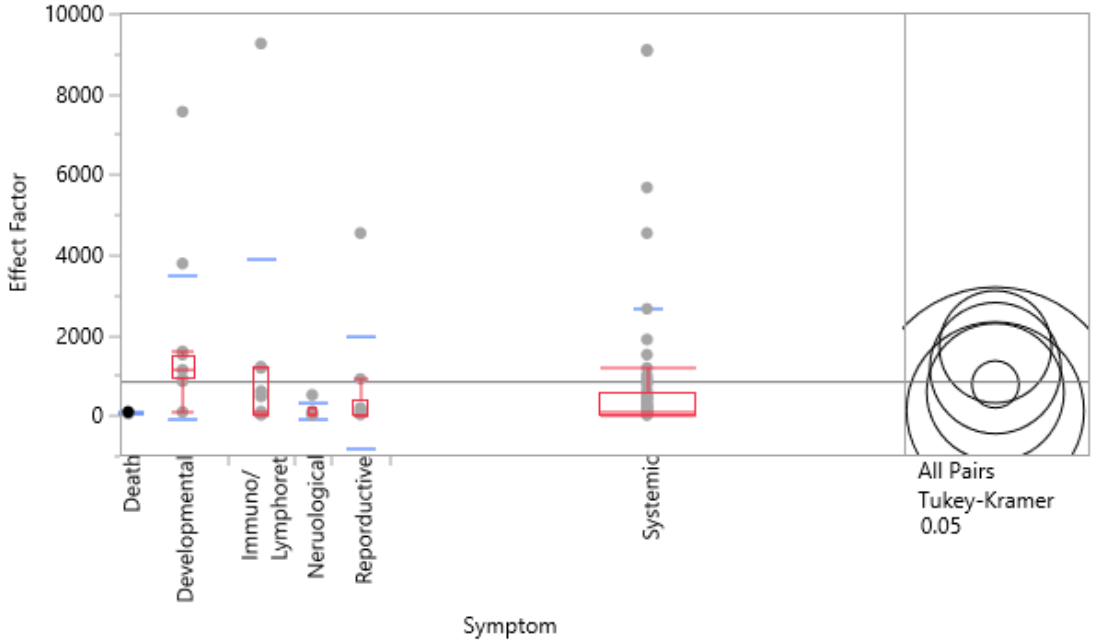
Assuming unequal variances

Difference	34.70	t Ratio	0.113818
Std Err Dif	304.85	DF	91.79477
Upper CL Dif	640.17	Prob > |t|	0.9096
Lower CL Dif	-570.78	Prob > t	0.4548
Confidence	0.95	Prob < t	0.5452



Fit Group

Oneway Analysis of Effect Factor By Symptom



Oneway Anova

Summary of Fit

Rsquare	0.040862
Adj Rsquare	0.002187
Root Mean Square Error	1869.329
Mean of Response	852.295
Observations (or Sum Wgts)	130

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Symptom	5	18459769	3691954	1.0565	0.3878
Error	124	433304376	3494390		
C. Total	129	451764145			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Death	3	67.17	1079.3	-2069	2203.3
Developmental	15	1705.31	482.7	750	2660.6
Immuno/ Lymphoret	11	1175.34	563.6	60	2290.9
Neruological	6	116.13	763.2	-1394	1626.6
Reporductive	10	579.33	591.1	-591	1749.3
Systemic	85	771.75	202.8	370	1173.1

Std Error uses a pooled estimate of error variance

Means Comparisons

Comparisons for all pairs using Tukey-Kramer HSD

Confidence Quantile

q*	Alpha
2.89478	0.05

Fit Group

Oneway Analysis of Effect Factor By Symptom

Means Comparisons

Comparisons for all pairs using Tukey-Kramer HSD

HSD Threshold Matrix

Abs(Dif)-HSD

	Developmental	Immuno/ Lymphoret	Systemic	Reporductive	Neruological	Death
Developmental	-1975.9	-1618.1	-581.9	-1083.2	-1024.7	-1784.3
Immuno/ Lymphoret	-1618.1	-2307.4	-1330.3	-1768.4	-1687.1	-2416.4
Systemic	-581.9	-1330.3	-830.1	-1616.6	-1630.2	-2474.3
Reporductive	-1083.2	-1768.4	-1616.6	-2420.0	-2331.2	-3050.0
Neruological	-1024.7	-1687.1	-1630.2	-2331.2	-3124.2	-3777.4
Death	-1784.3	-2416.4	-2474.3	-3050.0	-3777.4	-4418.3

Positive values show pairs of means that are significantly different.

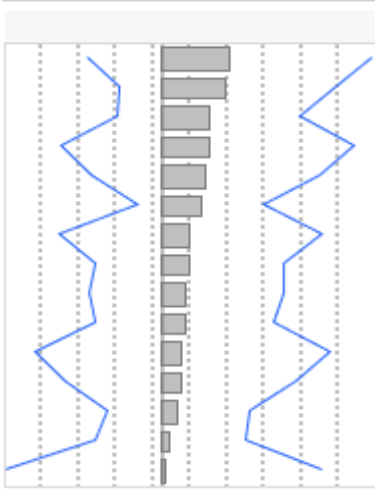
Connecting Letters Report

Level		Mean
Developmental	A	1705.3052
Immuno/ Lymphoret	A	1175.3376
Systemic	A	771.7466
Reporductive	A	579.3277
Neruological	A	116.1323
Death	A	67.1741

Levels not connected by same letter are significantly different.

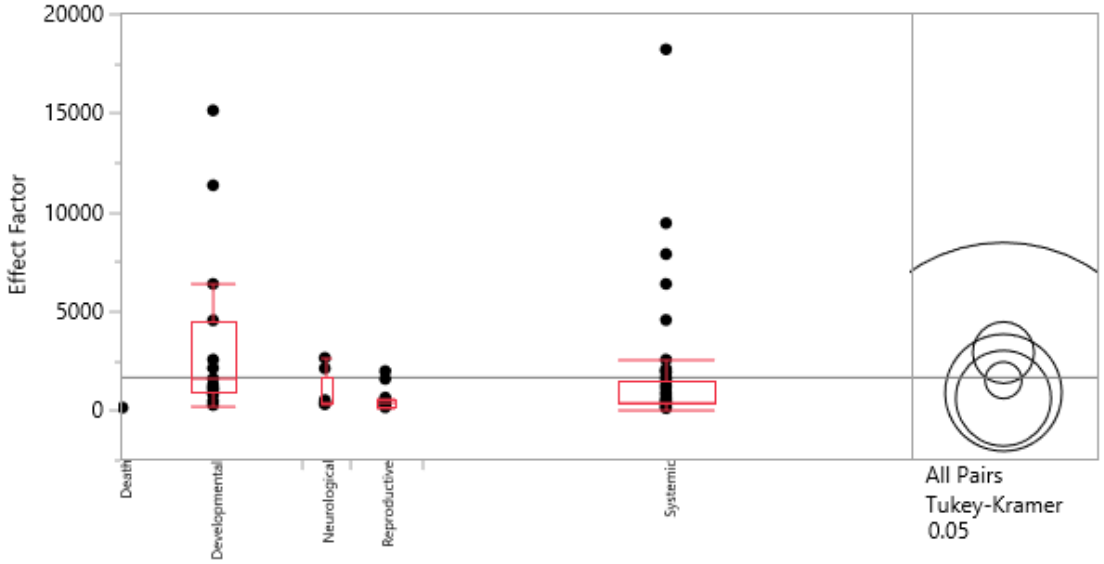
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Developmental	Death	1638.131	1182.267	-1784.28	5060.538	0.7356
Developmental	Neruological	1589.173	902.972	-1024.73	4203.079	0.4953
Developmental	Reporductive	1125.977	763.150	-1083.18	3335.132	0.6805
Immuno/ Lymphoret	Death	1108.163	1217.567	-2416.43	4632.754	0.9433
Immuno/ Lymphoret	Neruological	1059.205	948.720	-1687.13	3805.544	0.8737
Developmental	Systemic	933.559	523.517	-581.91	2449.026	0.4803
Systemic	Death	704.572	1098.138	-2474.30	3883.443	0.9876
Systemic	Neruological	655.614	789.626	-1630.18	2941.409	0.9614
Immuno/ Lymphoret	Reporductive	596.010	816.769	-1768.36	2960.377	0.9779
Developmental	Immuno/ Lymphoret	529.968	742.045	-1618.09	2678.027	0.9799
Reporductive	Death	512.154	1230.543	-3050.00	4074.307	0.9984
Reporductive	Neruological	463.195	965.317	-2331.19	3257.579	0.9968
Immuno/ Lymphoret	Systemic	403.591	598.984	-1330.34	2137.520	0.9845
Systemic	Reporductive	192.419	624.940	-1616.65	2001.483	0.9996
Neruological	Death	48.958	1321.815	-3777.41	3875.325	1.0000



Fit Group

Oneway Analysis of Effect Factor By Symptom



Symptom

Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
Death	127.3569	127.3569	127.3569	127.3569	127.3569	127.3569	127.3569
Developmental	226.7574	226.7574	851.505	1591.961	4535.147	6367.844	15117.16
Neurological	299.6632	299.6632	328.7354	400.8277	1709.385	2636.714	2636.714
Reproductive	147.5476	162.9819	249.6661	414.9533	597.2846	1849.263	1967.301
Systemic	56.68934	147.5476	359.7652	408.1951	1573.841	2451.879	18193.84

Oneway Anova

Summary of Fit

Rsquare	0.055592
Adj Rsquare	0.025611
Root Mean Square Error	3010.398
Mean of Response	1686.065
Observations (or Sum Wgts)	131

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Symptom	4	67215478.5	16803870	1.8542	0.1226
Error	126	1141874790	9062498.3		
C. Total	130	1209090269			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Death	1	127.36	3010.4	-5830	6084.8
Developmental	29	2902.47	559.0	1796	4008.8
Neurological	8	879.37	1064.3	-1227	2985.7
Reproductive	12	599.30	869.0	-1120	2319.1
Systemic	81	1510.48	334.5	849	2172.4

Std Error uses a pooled estimate of error variance

Fit Group

Oneway Analysis of Effect Factor By Symptom

Means Comparisons

Comparisons for all pairs using Tukey-Kramer HSD

Confidence Quantile

q*	Alpha
2.76768	0.05

HSD Threshold Matrix

Abs(Dif)-HSD

	Developmental	Systemic	Neurological	Reproductive	Death
Developmental	-2188	-411	-1304	-557	-5699
Systemic	-411	-1309	-2457	-1666	-7000
Neurological	-1304	-2457	-4166	-3523	-8085
Reproductive	-557	-1666	-3523	-3401	-8200
Death	-5699	-7000	-8085	-8200	-11783

Positive values show pairs of means that are significantly different.

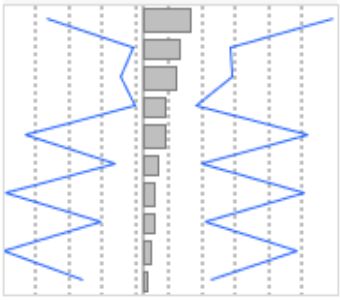
Connecting Letters Report

Level		Mean
Developmental	A	2902.4747
Systemic	A	1510.4793
Neurological	A	879.3735
Reproductive	A	599.2993
Death	A	127.3569

Levels not connected by same letter are significantly different.

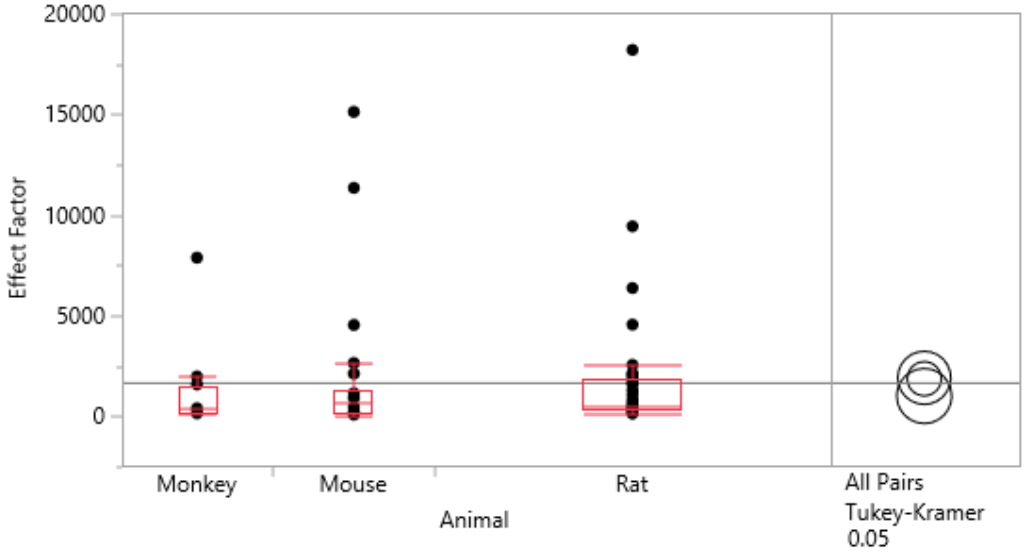
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Developmental	Death	2775.118	3061.862	-5699.13	11249.37	0.8940
Developmental	Reproductive	2303.175	1033.300	-556.67	5163.02	0.1759
Developmental	Neurological	2023.101	1202.211	-1304.23	5350.44	0.4482
Developmental	Systemic	1391.995	651.447	-411.00	3194.99	0.2112
Systemic	Death	1383.122	3028.924	-6999.97	9766.21	0.9909
Systemic	Reproductive	911.180	931.177	-1666.02	3488.38	0.8645
Neurological	Death	752.017	3193.010	-8085.21	9589.24	0.9993
Systemic	Neurological	631.106	1115.659	-2456.68	3718.89	0.9798
Reproductive	Death	471.942	3133.322	-8200.09	9143.97	0.9999
Neurological	Reproductive	280.074	1374.053	-3522.86	4083.01	0.9996



Fit Group

Oneway Analysis of Effect Factor By Animal



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
Monkey	147.5476	147.5476	147.5476	393.4603	1573.841	1967.301	7869.206
Mouse	56.68934	226.7574	226.7574	680.2721	1377.683	4535.147	15117.16
Rat	86.75537	221.2826	359.7652	509.4275	1872.895	6367.844	18193.84

Oneway Anova

Summary of Fit

Rsquare	0.013785
Adj Rsquare	-0.00162
Root Mean Square Error	3052.181
Mean of Response	1686.065
Observations (or Sum Wgts)	131

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Animal	2	16666937.9	8333469	0.8946	0.4113
Error	128	1192423331	9315807		
C. Total	130	1209090269			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
Monkey	28	1002.97	576.81	-138	2144.3
Mouse	30	1906.12	557.25	804	3008.7
Rat	73	1857.64	357.23	1151	2564.5

Std Error uses a pooled estimate of error variance

Means Comparisons

Comparisons for all pairs using Tukey-Kramer HSD

Confidence Quantile

q*	Alpha
2.37132	0.05

Fit Group

Oneway Analysis of Effect Factor By Animal

Means Comparisons

Comparisons for all pairs using Tukey-Kramer HSD

HSD Threshold Matrix

Abs(Dif)-HSD

	Mouse	Rat	Monkey
Mouse	-1868.8	-1521.1	-998.7
Rat	-1521.1	-1198.0	-754.2
Monkey	-998.7	-754.2	-1934.4

Positive values show pairs of means that are significantly different.

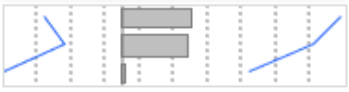
Connecting Letters Report

Level		Mean
Mouse	A	1906.1242
Rat	A	1857.6380
Monkey	A	1002.9724

Levels not connected by same letter are significantly different.

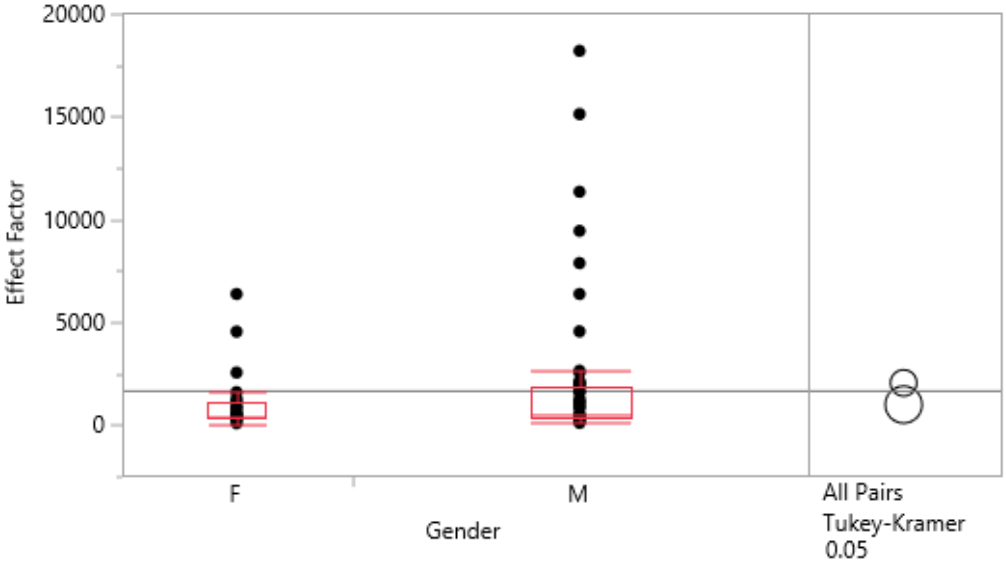
Ordered Differences Report

Level	- Level	Difference	Std Err Dif	Lower CL	Upper CL	p-Value
Mouse	Monkey	903.1518	802.0189	-998.69	2804.997	0.4998
Rat	Monkey	854.6656	678.4697	-754.20	2463.536	0.4206
Mouse	Rat	48.4862	661.9220	-1521.14	1618.116	0.9970



Fit Group

Oneway Analysis of Effect Factor By Gender



Quantiles

Level	Minimum	10%	25%	Median	75%	90%	Maximum
F	56.68934	226.7574	359.7652	408.1951	1077.098	2547.138	6367.844
M	86.75537	147.5476	359.7652	509.4275	1915.141	6367.844	18193.84

Oneway Anova

Summary of Fit

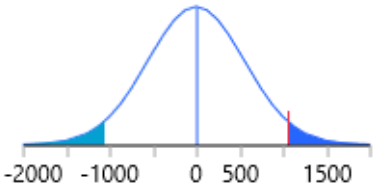
Rsquare	0.026949
Adj Rsquare	0.019406
Root Mean Square Error	3019.967
Mean of Response	1686.065
Observations (or Sum Wgts)	131

t Test

M-F

Assuming equal variances

Difference	1056.0	t Ratio	1.890177
Std Err Dif	558.7	DF	129
Upper CL Dif	2161.3	Prob > |t|	0.0610
Lower CL Dif	-49.4	Prob > t	0.0305*
Confidence	0.95	Prob < t	0.9695



Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Ratio	Prob > F
Gender	1	32584366.5	32584367	3.5728	0.0610
Error	129	1176505902	9120200.8		
C. Total	130	1209090269			

Means for Oneway Anova

Level	Number	Mean	Std Error	Lower 95%	Upper 95%
F	44	984.77	455.28	84.0	1885.5
M	87	2040.74	323.77	1400.1	2681.3

Std Error uses a pooled estimate of error variance

Fit Group

Oneway Analysis of Effect Factor By Gender

Means Comparisons

Comparisons for all pairs using Tukey-Kramer HSD

Confidence Quantile

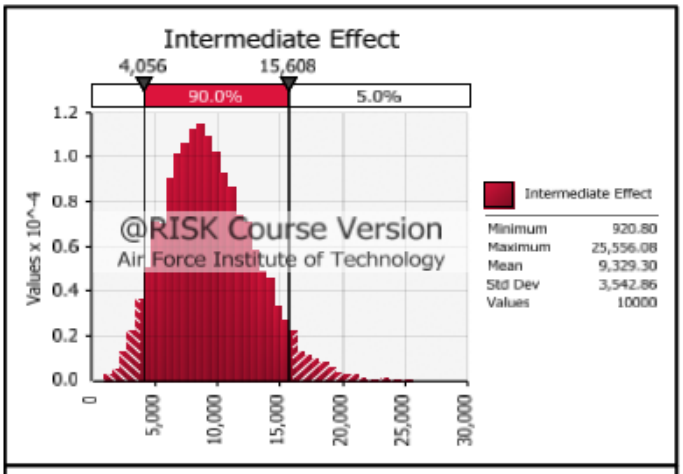
q*	Alpha
1.97852	0.05

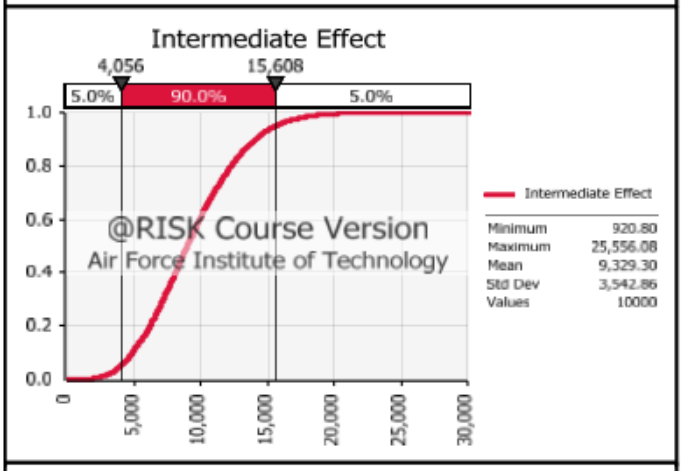
HSD Threshold Matrix

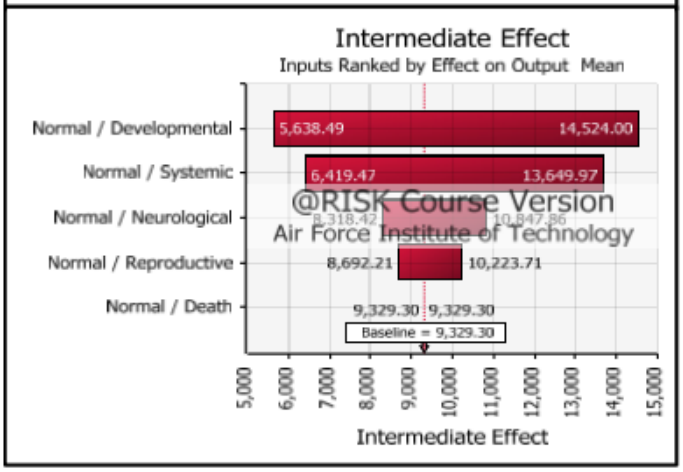
Abs(Dif)-HSD

	M	F
M	-905.9	-49.4
F	-49.4	-1273.9

Appendix C: Monte Carlo Results



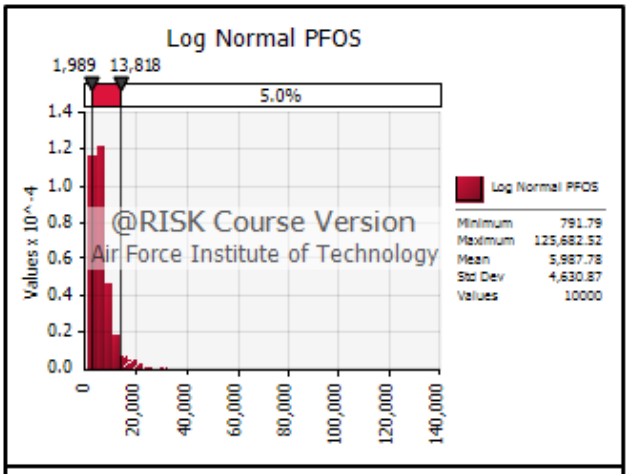


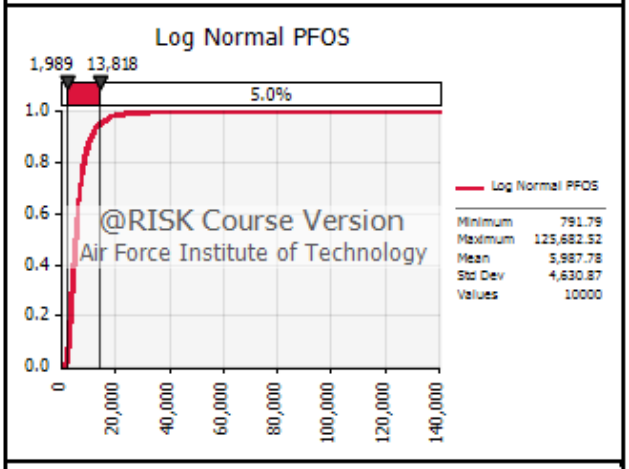


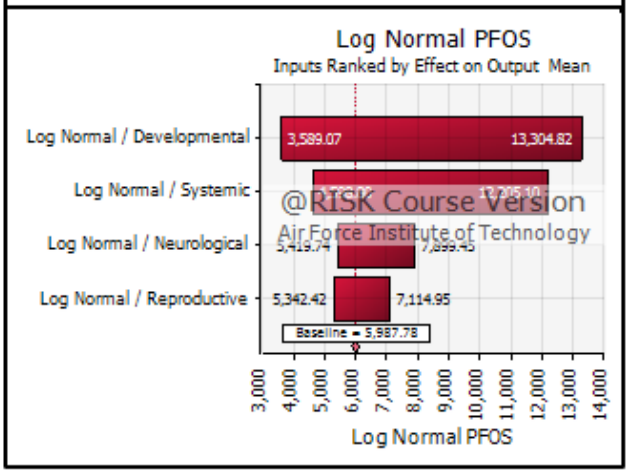
Simulation Summary Information	
Workbook Name	PFAS Effect Factor Data.xlsx
Number of Simulations	1
Number of Iterations	10000
Number of Inputs	21
Number of Outputs	4
Sampling Type	Monte Carlo
Random # Generator	Mersenne Twister
Random Seed	348598706

Summary Statistics for Intermediate Effect			
Statistics		Percentile	
Minimum	920.8034085	5%	4056.014148
Maximum	25556.07588	10%	4894.440073
Mean	9329.300155	15%	5629.012919
Std Dev	3542.863263	20%	6221.352808
Variance	12551880.1	25%	6754.785008
Skewness	0.452225679	30%	7227.318246
Kurtosis	3.014309074	35%	7694.087985
Median	9011.629383	40%	8131.998459
Mode	9912.459334	45%	8573.026528
Left X	4056.014148	50%	9011.629383
Left P	5%	55%	9467.237855
Right X	15607.76192	60%	9949.37681
Right P	95%	65%	10465.15275
Diff X	11551.74777	70%	11035.50902
Diff P	90%	75%	11637.62497
#Errors	0	80%	12315.73123
Filter Min	Off	85%	13094.93858
Filter Max	Off	90%	14117.8344
#Filtered	0	95%	15607.76192

Change in Output Statistic for Intermediate Effect			
Rank	Name	Lower	Upper
1	Normal / Developm	5638.494283	14524.00434
2	Normal / Systemic	6419.473498	13649.96641
3	Normal / Neurologi	8318.422013	10847.86182
4	Normal / Reproduct	8692.211156	10223.71004
5	Normal / Death	9329.300155	9329.300155



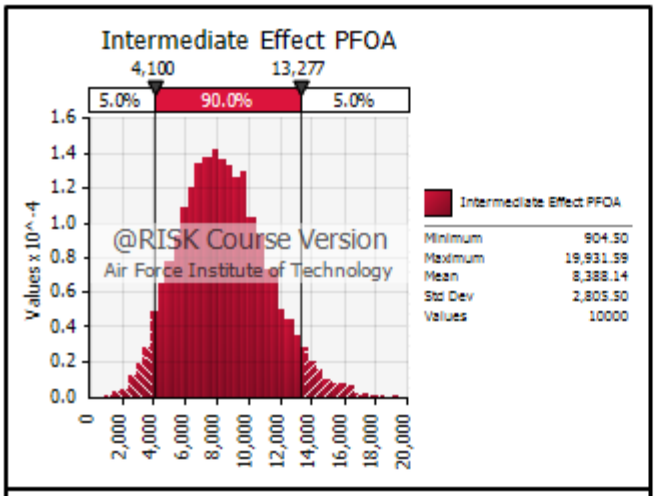


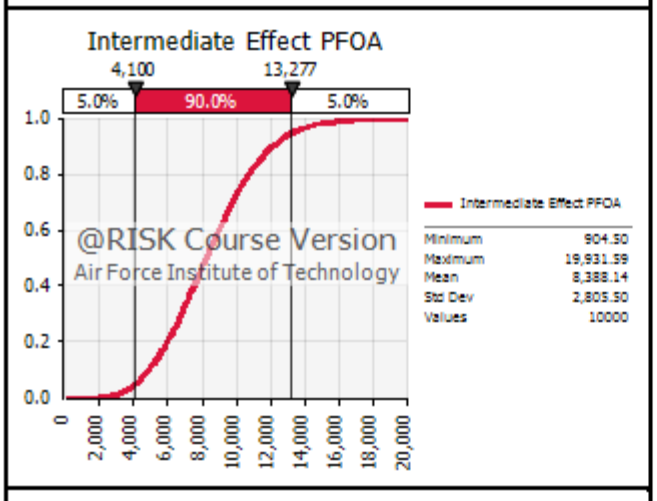


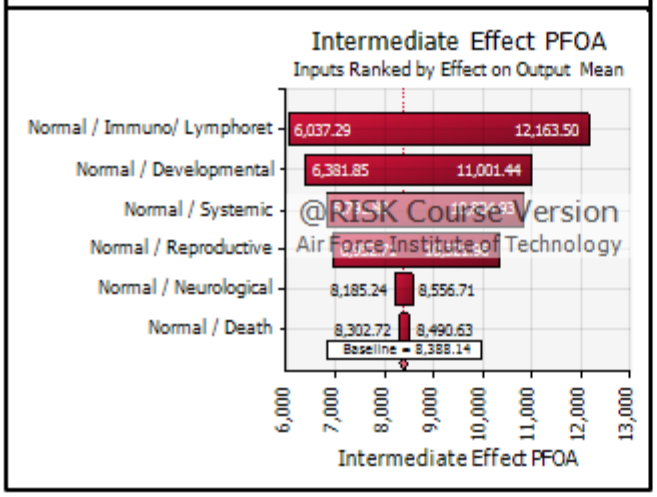
Simulation Summary Information	
Workbook Name	Thesis Data For Monte
Number of Simulations	1
Number of Iterations	10000
Number of Inputs	21
Number of Outputs	4
Sampling Type	Monte Carlo
Random # Generator	Mersenne Twister
Random Seed	348598706

Summary Statistics for Log Normal PFOS			
Statistics		**Percentile**	
Minimum	791.7930079	**5%**	1989.458
Maximum	125682.5196	**10%**	2376.091
Mean	5987.777669	**15%**	2702.736
Std Dev	4630.869852	**20%**	2985.992
Variance	21444955.59	**25%**	3279.677
Skewness	5.321796822	**30%**	3558.241
Kurtosis	79.6872421	**35%**	3850.972
Median	4794.050023	**40%**	4155.876
Mode	2963.702456	**45%**	4463.677
Left X	1989.458091	**50%**	4794.05
Left P	5%	**55%**	5170.83
Right X	13818.38083	**60%**	5567.173
Right P	95%	**65%**	6026.292
Diff X	11828.92274	**70%**	6563.564
Diff P	90%	**75%**	7167.499
#Errors	0	**80%**	7996.538
Filter Min	Off	**85%**	9032.519
Filter Max	Off	**90%**	10663.67
#Filtered	0	**95%**	13818.38

Change in Output Statistic for Log Normal PFOS			
Rank	**Name**	**Lower**	**Upper**
1	Log Normal / Developmenta	3589.07	13304.82
2	Log Normal / Systemic	4598.797	12205.1
3	Log Normal / Neurological	5419.741	7899.454
4	Log Normal / Reproductive	5342.422	7114.952



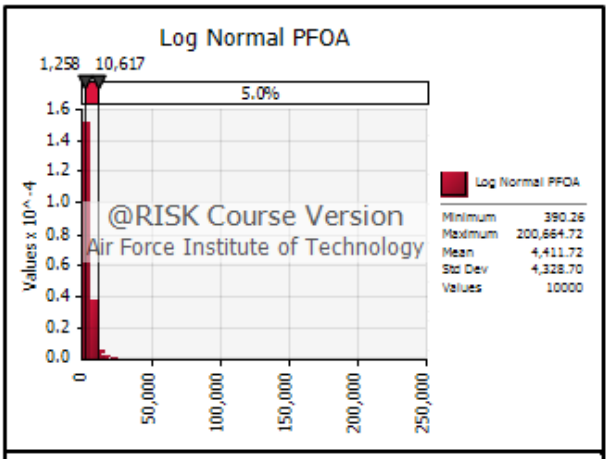


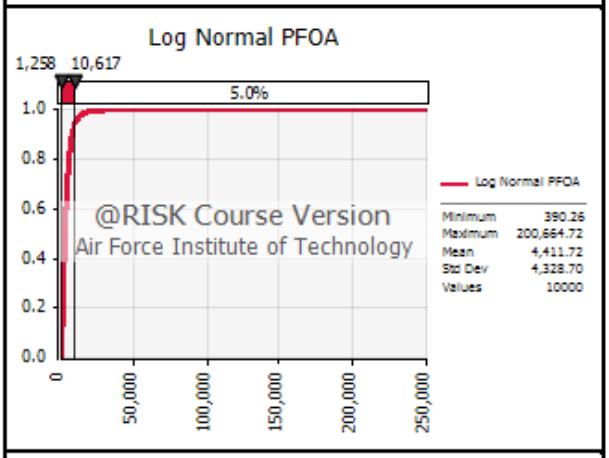


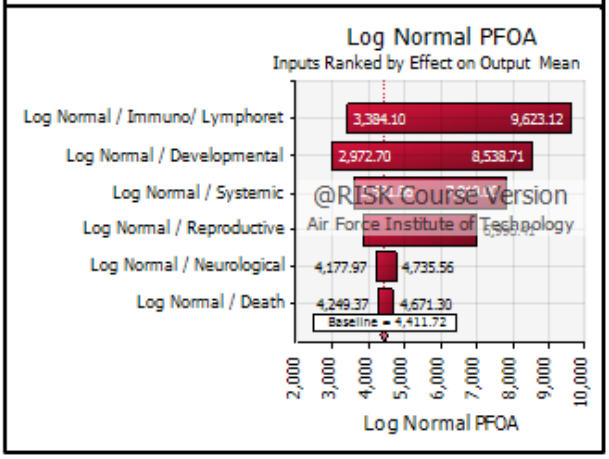
Simulation Summary Information	
Workbook Name	Thesis Data For Monte
Number of Simulations	1
Number of Iterations	10000
Number of Inputs	21
Number of Outputs	4
Sampling Type	Monte Carlo
Random # Generator	Mersenne Twister
Random Seed	348598706

Summary Statistics for Intermediate Effect PFOA			
Statistics		**Percentile**	
Minimum	904.5041645	**5%**	4100.156
Maximum	19931.58769	**10%**	4862.977
Mean	8388.136503	**15%**	5460.91
Std Dev	2805.50349	**20%**	5929.412
Variance	7870849.834	**25%**	6372.608
Skewness	0.35968453	**30%**	6770.124
Kurtosis	3.027723936	**35%**	7137.125
Median	8228.656649	**40%**	7495.188
Mode	8485.013078	**45%**	7870.545
Left X	4100.156041	**50%**	8228.657
Left P	5%	**55%**	8593.368
Right X	13276.50859	**60%**	8956.29
Right P	95%	**65%**	9360.163
Diff X	9176.352549	**70%**	9747.709
Diff P	90%	**75%**	10185.94
#Errors	0	**80%**	10716.88
Filter Min	Off	**85%**	11337.46
Filter Max	Off	**90%**	12082.08
#Filtered	0	**95%**	13276.51

Change in Output Statistic for Intermediate Effec			
Rank	**Name**	**Lower**	**Upper**
1	Normal / Immun	6037.295	12163.5
2	Normal / Develo	6381.854	11001.44
3	Normal / Systen	6791.802	10834.93
4	Normal / Reprod	6952.709	10321.96
5	Normal / Neurol	8185.242	8556.706
6	Normal / Death	8302.724	8490.631







Simulation Summary Information	
Workbook Name	Thesis Data For Monte
Number of Simulations	1
Number of Iterations	10000
Number of Inputs	21
Number of Outputs	4
Sampling Type	Monte Carlo
Random # Generator	Mersenne Twister
Random Seed	348598706

Summary Statistics for Log Normal PFOA			
Statistics		**Percentile**	
Minimum	390.2577112	**5%**	1258.247
Maximum	200664.7238	**10%**	1555.029
Mean	4411.720009	**15%**	1802.053
Std Dev	4328.695433	**20%**	2014.783
Variance	18737604.15	**25%**	2233.4
Skewness	12.93601173	**30%**	2434.17
Kurtosis	460.0270699	**35%**	2655.912
Median	3394.075072	**40%**	2879.046
Mode	2452.102966	**45%**	3127.827
Left X	1258.246767	**50%**	3394.075
Left P	5%	**55%**	3696.294
Right X	10616.90998	**60%**	3991.538
Right P	95%	**65%**	4350.558
Diff X	9358.663212	**70%**	4773.433
Diff P	90%	**75%**	5284.405
#Errors	0	**80%**	5910.137
Filter Min	Off	**85%**	6731.571
Filter Max	Off	**90%**	7967.181
#Filtered	0	**95%**	10616.91

Change in Output Statistic for Log Normal PFOA			
Rank	**Name**	**Lower**	**Upper**
1	Log Normal / Immuno/ Lymphore	3384.096	9623.124
2	Log Normal / Developmental	2972.696	8538.714
3	Log Normal / Systemic	3581.858	7819.004
4	Log Normal / Reproductive	3835.919	6996.407
5	Log Normal / Neurological	4177.967	4735.555
6	Log Normal / Death	4249.375	4671.295

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14. ABSTRACT

PFAS are man-made substances that are used as surfactants in industrial processes and commercial products most notably for the Air Force in AFFF. There are no regulatory treatment levels within the US. In order to fill this knowledge gap, I collected data of published research testing for dose-response. Using USEtox® software, I analyzed the data to obtain comparable toxic units (CTU) for several short and long chain PFAS including PFOA and PFOS then compared those values to the impacts of treatment technologies. This research found the optimal treatment level should be 10 and 13 parts per trillion for PFOA and PFOS respectively and that short chains are less hazardous than long chain PFAS.

15. SUBJECT TERMS

Per-, Polyfluoroalkyl substances (PFAS); Life Cycle Impact Analysis; Toxicology; Risk Assessment; USETox

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